Electronic monitoring devices in asthma: translating from study use into clinical practice

Ireti Deborah Adejumo MBChB MRCP

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy (2020)

Table of Contents

Abstract

Introduction

Asthma is increasingly recognised to be a heterogeneous disease with outcomes mediated by psychosocial and behavioural factors as well as by pathophysiological mechanisms. Inhaled corticosteroids (ICS) have long been the mainstay of treatment for asthma and poor ICS adherence has been shown to be associated with adverse outcomes. Despite this, poor ICS adherence has remained a persistent challenge for clinicians and patients with difficulties in both its measurement and management.

In recent times, electronic monitoring has emerged as a gold standard for adherence measurement and a possible interventional tool for poor adherence. This thesis aimed to assess trial evidence for the use of electronic monitoring devices (EMDs) in asthma and assess whether there was adequate justification for their widespread clinical uptake.

Methods

Two literature reviews were conducted. The first was a systematic review and meta-analysis of the use of EMDs to measure adherence in adult asthma studies. The second was a

review of the use of EMDs as interventional tools in both adults and children.

A randomised controlled pilot study of adherence was conducted to investigate the effect of EMD-based feedback in a real-world study design. As part of this, testing data for based on previously published validation protocols were also presented.

Finally, a series of semi-structured interviews were conducted to explore the experiences and perspectives of EMD users.

Results

The first literature review estimated population adherence to be 64% of prescribed ICS doses. The second review demonstrated that EMD-based interventions were effective at improving adherence but that evidence of improvement in clinical outcomes was not consistent.

Across all devices tested in the pilot study, 94% of actuation, installation and removal events were correctly detected pre-study. Despite this, 12% of devices failed pre-study testing. Of devices issued to study participants, a further 12% were found to have failed post-study.

The pilot study of adherence found that the intervention group actuated 11% more of their prescribed ICS doses than the control group (p=0.319). An unexpected increase in exacerbations in the intervention group suggested that the relationship between adherence and outcomes may be more complex than previously thought. Across the whole study, greater frequency of short-acting beta-agonist (SABA) use was associated with poorer asthma control (p=0.003), lower asthma-related quality of life (p=0.001), lower percentage predicted forced expiratory volume in one second (FEV_1, p=0.019) and an increased proportion of individuals suffering an exacerbation over the study period (p=0.038).

Finally, in a qualitative study, participants described their desire to feel in control of their asthma. EMDs were generally acceptable and some reported impact on their awareness and behaviours. For others, there were frustrations around perceived technical faults and concerns about data reliability. Future desirability centred on the potential impact of EMDs in helping users take control of their asthma, including through integrating with other wearable technology and enhancing self-monitoring.

Conclusion

Whilst inhaler monitoring technology holds significant promise in both identifying individuals with asthma who may benefit from targeted adherence intervention and as part of targeted adherence interventions, there remains concern with regards to their real-world reliability and inadequate evidence of their clinical benefit. This thesis puts forward considerations in both study and intervention design with the aim of building a better evidence base for their adoption into real-world use.

Funding

This PhD studentship was funded by an investigator-led grant from Glaxo-Smith-Kline.

List of abstracts and publications

Thematic Poster European Respiratory Society International Congress Sept 2017

Adejumo I, Patel M, McKeever TM, Shaw D. Electronic Monitoring Devices in Clinical Trials: A Doddle to Use? *ERJ*. 2017; 50(suppl61): PA3957.
DOI: 10.1183/1393003.congress-2017.PA3957

Thematic Poster European Respiratory Society International Congress Sept 2018

Adejumo I, Shaw D. Electronic monitoring devices: the saviour of poor control in asthma? *ERJ.* 2018; 52(suppl62): PA4443.
DOI: 10.1183/13993003.congress-2018.PA4443

Publications

Adejumo I, Shaw DE. Electronic monitoring devices as an intervention in Asthma: The story so far. *Current Respiratory Medicine Reviews* 2018. 14(1):5-22.

Acknowledgements

Firstly, my thanks to my supervisory team. Professor Dominick Shaw, thank you for taking a chance on me and for your expert (and patient) guidance through the ups and downs of this project. Professor Tricia McKeever, thank you for your indomitable statistical expertise, for reminding me to take care of myself and for your advocacy during a global pandemic. Dr Manpreet Bains, thank you for your help in taking a qualitative novice all the way through from study design to study completion.

My thanks also to Dr Mitesh Patel who conceived the original idea for the pilot study and whose institutional memory with regards to using the Smartinhaler™ system proved invaluable.

Norma Thompson, thank you for teaching me almost everything I know about running a study. Your eagle eye and attention to detail have saved me more than once. Glenn Hearson, thank you for your database (and general IT) expertise and the hours of re-editing and data validating.

Mohammad Ali, Tina Wilkinson, Charlotte Dobson, thank you all for your help with recruitment. Thanks also to Professor Harrison and Shani Hutchinson for your help in offering primary care recruitment expertise. To all the staff at NRRU – Katherine

Smith, Liz Dark, Nicola Neesham, Karen Shaw for the ideas, cups of tea and chocolate. Clair Parrish, thank you for stepping in last-minute to help with the study.

My thanks to the 36 individuals who volunteered their time and effort to participate in our pilot study.

To the clinical PhD cohort for their collective encouragement – Amanda Goodwin, Sarah Forster, Karmel Webb, Hannah Lawrence, Queenie Pang - thank you all. Thanks to all the housemates who have provided immeasurable empathy and a listening ear – Kathryn Osborne, Melisa Zulu, Miriam Burroughs, Helen MacKenzie.

Finally, I dedicate this thesis to my parents, Dr Goke Adejumo (proof-reader *par excellence)* and Toni Adejumo – for your unwavering belief and sacrificial love for which I will be forever grateful.

List of Tables

List of Figures

Chapter 1: Introduction

1.1. Asthma: characterisation and management

1.1.1. Epidemiology of asthma

The Global Initiative for Asthma (GINA) guidelines state that asthma is, "*a heterogeneous disease, usually characterized by chronic airway inflammation… defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation* (1)." Like many attempts, this definition relies heavily on the clinical features of asthma. Other definitions lay greater emphasis on the underlying pathophysiology features of reversible airflow obstruction, airway hyper-responsiveness and airway inflammation (2). Crucially, however, there are discrepancies between clinical and pathophysiological features (3, 4). There is also an absence of a universal biomarker (5). Thus, whilst definitions such as the one above are commonly quoted, they are also agreed to be insufficient for determining diagnosis and management (2, 5-8).

A recent study estimated the global prevalence of asthma at 358.2 million people, a 12.6% increase between 1990 and 2015 (9). Asthma UK have previously estimated that around 5.4 million people are being treated for asthma in the United

Kingdom (1.1 million children and 4.3 million adults) (10). The Department of Health's 2011 estimate was that treating asthma costs the NHS around £1 billion, not accounting for wider societal costs such as lost productivity. It also estimated that around 1000 people die from their asthma in the UK every year (11). In 2014, the National Review of Asthma Deaths (NRAD) published by the Royal College of Physicians found that asthma resulted in 65 000 hospital admissions between 2011 and 2012. It found 900 deaths met the inclusion criteria for asthma as the underlying cause and concluded that 65% of the 195 deaths eventually reviewed had *"factors that could have avoided the death related to patients, their families and the environment…"* One of these factors was poor adherence to asthma treatment (12).

1.1.2. Characterising asthma

The way asthma is understood is changing (13). A 2018 Lancet Commission argues that it is no longer adequate to describe the clinical syndrome without attempting to characterise the underlying mechanisms at play. The authors join others in advocating a move away from offering all patients with a diagnosis of asthma a common treatment pathway (5, 14, 15). In place of these models, they advocate an *"era of asthma management, which accounts for the increasingly recognised*

heterogeneity of asthma and offers precision management and targeted treatment on the basis of careful assessment of the characteristics of a patient's disease." (5)

The concept of asthma as being more than a single entity is not new. Asthma was previously subdivided into "*extrinsic asthma"* (associated with an early age of onset and atopic features) and *"intrinsic asthma"* (older age of onset and an absence of allergic features) (16). This paradigm is now considered to be an oversimplification, however condensing the various known pathways into formal subgroups remains challenging (8).

Unbiased techniques (such as cluster analysis and transcriptomics) are providing clues to phenotypes ("*observable characteristics… [resulting] from interaction between… genes and the environment" (17)*) that fit with emerging molecular pathways (18-20). However, these data also suggest that a significant proportion of individuals experience disease that is not easily explained. Haldar et al., for example demonstrated that some individuals with a high symptom burden experienced few exacerbations and had low inflammatory markers. In contrast, other individuals had a low symptom burden but frequent exacerbations and marked eosinophilia (3).

As acceptance of asthma's biological complexity has grown, so, in turn, has the recognition that it interacts heavily with the individuals' comorbidities, psychosocial status, behaviours and environment (5). The movement of treatment models towards personalisation is therefore not exclusive to molecular mechanisms (14, 15, 21). A 'treatable traits' model proposes that whilst atopy, for example, may be a key driver for disease in one person, smoking may be a key driver for disease in another and comorbid depression a key driver for poor control in yet another. As a result, there is a developing interest in characterising these disease-external factors in addition to characterising the disease itself. A recent post-hoc analysis of the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) cohort (421 severe asthma, 88 mild/moderate asthma) demonstrated the applicability of the treatable traits model both for biological phenotypes (such as atopy, fixed airflow obstruction and reversibility) and, importantly, for adherence (22).

Guidelines from the British Thoracic Society and Scottish Intercollegiate Network (BTS/SIGN), GINA and the European Respiratory and American Thoracic Societies (ERS/ATS) are moving to reflect this new paradigm (1, 6, 21). They acknowledge that 'non-disease' factors impact the success of

pharmacological approaches. They further recommend the systematic targeting of these factors, particularly where there is apparent resistance to usual care.

Summarily, as our understanding of asthma's underlying pathophysiology evolves to account for its heterogeneity and complexity, an approach to asthma as a purely biological process appears increasingly obsolete. The centrality of searching for both prevention and cure, of greater aetiological understanding and of drug development is without debate. However, additional engagement with behavioural and psychosocial factors will prove important if progress in asthma outcomes is to be seen (5, 15, 23).

1.1.3. Concepts in asthma diagnosis and management

For a significant period of time, the diagnosis of asthma has been based on the presence of persistent symptoms and the ability to demonstrate reversible airflow obstruction (6). In the United Kingdom's (UK) primary care system, a pragmatic approach is often taken, involving trials of treatment and observed response (6, 7). The response may either be subjective or objective with peak flow diaries and/or spirometry (6). However it is well recognised that this is a broad brush, with the NRAD in the UK noting that 10% of the 276 cases which were eventually reviewed for possible inclusion by the enquiry

were deemed unlikely to have ever had true asthma (12) and another study that a third of patients in primary care with an asthma diagnosis had no evidence of any physiological airway abnormality (reversibility or hyper-responsiveness) (4). Consequently, a system of supportive diagnostic features has developed where evidence of airway inflammation (sputum eosinophilia, serum eosinophilia and fractional exhaled nitric oxide [F_ENO]), airway hyper-responsiveness (e.g. methacholine challenge testing) or atopy (IgE levels, skin prick testing) may be included to fortify the case for diagnosis (6, 7).

Whatever the journey to diagnosis, the treatment pathway has remained the same. Individuals are commenced on low-dose inhaled corticosteroids (ICS) and treatment is titrated in a step-wise fashion with increasing doses or addition of adjuvant therapies depending on either response to treatment or new evidence of loss of control (6, 24). Traditionally, continuous oral corticosteroid therapy was used in severe disease which remained uncontrolled despite optimisation of other therapies. This came with a heavy side effect profile, particularly of metabolic disorders such as steroid-induced hyperglycaemia and osteoporosis (25). In recent years, however, the developing understanding of asthma's varying underlying molecular mechanisms has begun to give rise to molecular-

targeted therapies (5, 26), some of which had initially been discounted as ineffective because of the lack of targeting in early trials (27).

Recent developments notwithstanding, ICS remains the mainstay of therapy in asthma (6) with a well-described role in controlling airway inflammation (28) and improving outcomes in asthma (29). National and international reports credit the fall in asthma mortality in the 1990s/2000s to the increased uptake in ICS (5, 9). It is therefore unsurprising that ICS underuse has been linked with poor outcomes in asthma, including increased risk of exacerbation, hospitalisation and mortality (12, 30-33). The wealth of evidence has led to clarified definitions of uncontrolled asthma which emphasise the importance of adherence assessment in this group of patients (21). The term 'difficult asthma' is now preferred for asthma that remains uncontrolled despite apparently optimal standard therapy. This permits differentiation between inadequate medications adherence, for example, from truly refractory asthma. Furthermore, as clinical practice takes steps into the era of personalised medicine driven by the availability of high-cost, molecular-targeted therapies, both guideline groups and commissioners acknowledge that adherence management must play a greater role in the management of asthma (1, 6, 21, 34).

1.2. Concepts in adherence

1.2.1. Defining adherence

The World Health Organization's (WHO) 2003 report defines adherence as, "*the extent to which a person's behaviour… corresponds with agreed recommendations from a health care provider*" (35). Although the onus for directing behaviour is laid with the health professional, the report argues that there is an expectation of patient agreement. Adherence is thus differentiated from 'compliance', which implies unquestioning conformity.

Adherence (or non-adherence) may be measured in several ways, dependent on its stage. Initiation (or primary non-adherence) refers to whether the prescribed drug was ever commenced. Implementation (or secondary non-adherence) refers to whether the drug was taken as prescribed. Persistence (or tertiary non-adherence) refers to whether the drug was taken for the duration prescribed or prematurely stopped (35, 36). The generally accepted metric of implementation adherence across contemporary studies is the amount of drug presumed taken as a proportion of the dose prescribed (37), often presented as a percentage.

In some adherence studies, adherence (including implementation adherence) is described in binary terms, i.e. adherence vs. non-adherence. This belies the fact that adherence is a continuum. Whilst some patients may take all or none of their medication as prescribed, most are more likely to take varying proportions of their prescribed doses (38). Steiner et al. argue that even the representation of adherence as a continuum is an oversimplification. Adherence behaviours, rather than being constant, may be interrupted in a calculated manner (a therapeutic break for example, where a patient takes no medication for a defined period of time but takes it as prescribed outside of this window), in a regular but unintended manner (e.g. shift patterns influencing when doses are missed) or accidentally, such that the *pattern* of use is as informative as the percentage of use (39, 40).

Recommended levels of 'good' adherence tend to derive from the outcome sought, whether symptom control, disease control, reduction of future risk, or reduction of population risk. These parameters themselves depend both on the disease and the dose-response curve of the drug in question. In the case of human immunodeficiency virus (HIV), for example, studies suggest that a 95% adherence rate is required to achieve viral load suppression (35). In the case of hypertension, the

adherence level required for adequate disease control is likely to be lower (41).

1.2.2. The problem of medications non-adherence

In *Decorum*, the writer, thought to be Hippocrates, cautions, *"Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die. What they have done never results in a confession, but the blame is thrown upon the physician"* (37, 42). Some 2500 years later, the dilemma of how to persuade the patient into better health persists (37). Estimates of non-adherence range from 20-50% across chronic diseases (35, 37, 43-45). These estimates are drawn from papers going back as far as the 1970s. A Cochrane review on ICS adherence by Normansell, Kew and Stovold suggested that, in studies examining education as an intervention, adherence rates in control participants were 46.7% when measured objectively and 57.1% when subjective measures were included (46). Despite decades of adherence intervention research, the rates of non-adherence to medications are not changing.

Across chronic diseases overall, the evidence consistently suggests that poor adherence results in poorer outcomes for the patient and increased costs for healthcare systems (35, 38,

45). One review author quoted in a WHO report stated that, *"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments"* (35). In the United States, the cost of poor adherence to medication is thought to be approximately $100 billion per year (38). This may well be a conservative estimate (45). The risk remains that patients frequently come to harm, not because of a lack of scientific breakthrough, but because of a lack of uptake of existing interventions. The resultant hypothesis – that improving adherence will result in improved outcomes – is the basis of adherence research (37).

1.2.3. The relationship between adherence and outcomes

Of course, the relationship between adherence and outcomes is not straightforward. It is modified by the drug regimens involved, the way adherence is measured and the underlying disease (45). Furthermore, the fact a patient's beliefs are contrary to their physician's does not necessarily mean that they are wrong. One group of authors use the example of hypertension, where an estimated 19-43% achieve control despite reduced adherence, suggesting that treatment had been prescribed at a higher dose than required (39). Adherence will consequently only be a barrier to good outcomes where:

1. **Prescribed treatment is appropriate to the outcome sought.** For example, it has been speculated that, in a subset of individuals with a diagnosis of asthma but no evidence of steroid responsiveness, ICS may be ineffective (5, 8). Were this argument to be taken to its logical conclusion, ICS non-compliance in these individuals would not lead to worsened outcomes.
2. **Treatment is prescribed at the dose required to deliver the outcome sought.** It has been proposed that many patients with asthma are over-treated with higher doses of inhaled corticosteroids than required for their level of pathology (47). Beasley's group have previously shown that most of the effect of inhaled corticosteroid is likely to be achieved at 200 micrograms of fluticasone per day (roughly equivalent to 400 micrograms of beclometasone diproprionate [BDP]) (48). Beyond 500 micrograms of fluticasone (1000 micrograms of BDP), there is unlikely to be any additional benefit (49). Thus, poor adherence to overdosing regimes may not necessarily lead to worsened outcomes.
3. **Outcomes are influenced by factors other than the target disease.** The role of comorbidities in asthma, particularly in severe disease, is well-recognised. Conditions such as bronchiectasis, inducible laryngeal obstruction or

gastro-oesophageal reflux may mimic asthma symptoms (15, 21). In these circumstances, increased adherence to higher doses of ICS will not contribute to better outcomes until the relevant comorbidity has been addressed.

These factors impact the observed effectiveness of adherence interventions such that a difference in adherence may not necessarily equate to a difference in outcomes (45). Consequently, it may be more accurate to surmise that only where the appropriate drug is prescribed for the appropriate condition in the appropriate patient at the required dose will poor adherence be a true barrier to good outcomes.

1.2.4. Overview of medications adherence in asthma

Rates of inadequate ICS adherence in asthma are difficult to measure. Using a variety of means over the years, adherence has been quoted as ranging from as little as 22% to as high as 63%, largely dependent on study design and context (50). Although electronic monitoring is increasingly seen as the gold standard (6), this is a more recent development (38, 51).

In addition to difficulty measuring adherence, demonstrating the effect of poor adherence on clinical outcomes is complicated by challenges specific to the diagnosis and management of asthma. These challenges are the absence of a gold-standard

diagnostic test (6), difficulties in targeting certain treatments due to an incomplete understanding of underlying pathophysiological mechanisms and difficulties titrating treatment in the absence of biomarkers that correlate directly and consistently in a dose-responsive manner (48, 49). These challenges distinguish asthma from chronic conditions such as HIV and diabetes where there are clear diagnostic criteria and biomarkers which correlate directly with treatment response and outcomes (CD4 counts, capillary glucose, HbA1c).

Williams et al. estimate (in an analysis of a cohort of 298 predominantly African American participants) that 24.4% of exacerbations (oral steroids, emergency department [ED] visits and hospitalisations) may have been prevented by good ICS adherence. They further report that an estimated adherence level from their cohort of 75% was required to reduce the risk of exacerbations in uncontrolled (Asthma Control Test™ [ACT™] ≤19) asthma (32). Thus, whatever the challenges in diagnosis and treatment, there can be little doubt that encouraging higher levels of adherence in patients with asthma is central to improving outcomes (52).

1.2.5. Barriers to adherence

There has been a shift in recent times towards encouraging collaborative approaches for identifying and overcoming

barriers to adherence (39, 53). As a starting-point to understanding these barriers, a framework of intentional and unintentional non-adherence has been proposed (43). They are defined as follows:

Intentional non-adherence: *the patient decides not to take the medication or to take it in a way that differs from the recommendations…*

Unintentional non-adherence: *the patient is prevented from implementing their intention to take the medication, as prescribed, by factors beyond their control… (53)*

Horne argues that the absence of conceptually differentiating between these distinct categories is part of the reason adherence interventions have had limited success to date (43, 53). He instead advocates an approach which acknowledges that causes for poor adherence are complex and varied, an interaction between a person's subconscious beliefs, outside factors and conscious decisions (43).

An example framework for identifying intentional barriers would be the "*necessity-concerns framework*". According to this framework, individuals are thought to balance their beliefs about their personal need for ICS against concerns they may have such as perceptions of modern medicine, steroids or side

effects (53, 54). This particular framework finds support in adherence literature, with concerns around ICS safety, side effects and tolerance in particular consistently appearing across multiple studies (54-62). However also important are individuals' understandings of asthma as a chronic disease, of ICS and their person-level efficacy, readiness/motivation to take ICS, the influence of important others and trust in their physician (54-58, 60-62). An intervention that aims to modify beliefs on a larger scale requires such beliefs to be elicited and then targeted appropriately in a standardised manner (43, 62).

Unintentional non-adherence can be divided into patient-related factors, prescribing factors and system-related factors. With regards to patient factors, non-modifiable risk factors such as age, sex, socioeconomic factors and race-ethnicity have a contentious position in the literature (43). Beyond adolescence, increasing age appears to be consistently associated with better adherence across diseases (35, 62, 63). Associations between adherence and sex are less clear. Some studies show an association between female sex and poor adherence (63, 64). A large meta-analysis, however, shows an association between female sex and better adherence (45). Yet other studies suggest that young males are more likely to be lost to follow-up (62, 64).

The relationship between race-ethnicity is similarly unclear, having been shown to be mediated by personal beliefs and factors such as access to commercial health insurance, which are modifiable (56, 60, 62). Several authors therefore conclude that non-modifiable risk factors are unlikely to play a primary role in poor adherence and, where they do, this is likely to be mediated by risk factors (such as beliefs and socioeconomic factors) which are modifiable (43, 53, 62).

Forgetfulness is a commonly-cited modifiable adherence barrier (38). In children, an ordered family routine has been shown to be associated with both good inhaler refill and electronically monitored adherence as well as with well-controlled asthma (65, 66). Foster et al. (2012) found a positive association between routines *("I have a fixed daily routine for taking my asthma medications"/"I keep it somewhere where I will remember to take it")* and electronically monitored adherence (54). More recently, real-time reminder technology has been shown to improve adherence to ICS (67-71).

Somewhat unique to airways diseases is the role of technique in medication adherence. A recent meta-analysis of 144 studies estimated an overall prevalence of good technique in 31% of the population, acceptable technique in 41% of the population and poor technique in 31% of the population (72). New

research is demonstrating that inhaler technique may independently modify outcomes in asthma (73, 74), making such a high prevalence of poor technique problematic. Modification of inhaler technique is further challenging as the literature would suggest healthcare professionals' own understanding of inhaler technique is poor (75, 76). In addition to this, patients report that the time most healthcare providers are able to spend with them is often limited and infrequent (77), reducing the amount of time available to teach and reinforce technique.

Other modifiable patient factors include poor recall or comprehension of consultations where the drug and drug regimen have been explained and other additional advice given (53, 78, 79). There is a possibility this may be related to poor health literacy (37). Effective communication from the clinician and reiteration of what has been discussed, potentially through multiple media, are central to modifying these barriers (37, 39). Finally, there is a probable role for comorbidities, in particular depression (12, 43, 45, 56).

Several authors highlight the contribution of complex medication regimes to poor adherence (52, 78). Foster et al. reported that patients who forgot their evening doses had lower levels of adherence (54). Higher levels of device satisfaction, in

one study particularly related to physical characteristics, have also been associated with increased adherence (and improved outcomes) in asthma (80-82).

In systems where there is a lack of universal healthcare coverage, patients with lower income may find their socioeconomic status to be a barrier to adherence (37, 62, 83). Systems may also present barriers to communication such as inadequate appointment time for addressing adherence and lack of continuity of care (35, 37).

Overall, it is increasingly felt that silver-bullet solutions are unlikely to address the multifaceted nature of poor adherence. Comprehensive solutions addressing modifiable patient factors (including beliefs), disease/drug-specific factors and system factors are currently recommended to improve medications adherence and outcomes (35, 37). Some authors go even further, calling for a personalised approach to these factors (40, 53). Evidence for the effectiveness of complex behavioural interventions over more simple interventions in asthma, however, remains weak (46).

Research tools which may assist with a more holistic approach to barriers in medication use include the Beliefs about Medicines Questionnaire (BMQ), which is based on a necessity-concerns

framework (84) and the Adherence Starts with Knowledge questionnaires (ASK-20 and ASK-12), which incorporates questions to draw out factors such as beliefs, affect, motivation and health literacy (85, 86). The Hospital Anxiety Depression Scale (HADS) is a well-accepted measure of symptoms of mood disorders (87) which are known to influence not only adherence but outcomes in asthma (12, 56, 88). Other tools include the Medication Adherence Report Scale for Asthma (MARS-A) and Morisky Medication Adherence Scale (MMAS), which specifically look for indicators of non-adherence, although are less concerned with the reasons for this (89, 90).

1.2.6. Medication adherence: overuse

Sometimes forgotten in the conversation around adherence is the overuse of both ICS and bronchodilators. This is more frequently seen in bronchodilator overuse, probably because patients gain comparatively rapid onset symptomatic relief (91). However, bronchodilator overuse is an important risk factor for morbidity and mortality in asthma (92-94), most likely due to its role as a marker of poor asthma control (92, 95, 96) and of poor ICS adherence (97). This is recognised by asthma guidelines, leading to guidelines no longer recommending separate prescription of long-acting beta agonist (LABA) and ICS and more recently removing the use of

a short-acting beta agonist (SABA)-only approach to mild asthma (6, 98). Despite this, the 2014 NRAD report shows evidence that high reliever use has not always been detected or responded to by patients and their clinicians (12). ICS overuse is also a recognised phenomenon (99-101).

1.2.7. Adherence study design

Many attempts have taken place over decades to find reproducible, sustainable interventions which are implementable in the real world but which also improve adherence and outcomes. There is some evidence that interventions do improve adherence (102, 103), however this is not consistent and is dependent on both the intervention (104) and the disease (102). In their synthesis, Haynes et al. found a range of complex strategies including educational, behavioural and psychological strategies in varying combinations. Where interventions were demonstrated to be effective, the magnitude of the effect appeared outbalanced by the complexity of the intervention (103).

Despite the logical presumption that improvements in adherence and consequent effects on outcomes would have cost savings implications, this has not been well demonstrated in the literature (102). This latter is of particular importance in asthma as the BTS guidelines, whilst recognising electronic monitoring

as the gold-standard for adherence measurement in research, suggest that this is not yet translatable into the clinical arena due to its excessive cost (6).

In summary, adherence is not a concept that is easy to define. Poor adherence, primarily ICS underuse (and potentially including poor technique), is known to be associated with poor outcomes in asthma and SABA overuse is a marker of poor control. Reasons for poor adherence are complex and multifaceted. Adherence interventions should address them using a comprehensive approach which is both deliverable and clearly demonstrates effectiveness.

1.2.8. Adherence in this thesis

Unless otherwise specified, the term '*adherence'* is generally taken to refer to implementation adherence in the literature and will be similarly used in this thesis. Adherence is generally taken to mean the proportion of expected doses measured as taken by the individual. This thesis uses the term '*adherence'* recognising that it may describe a regime anywhere on a spectrum from clinician-imposed (compliance) to mutually agreed (concordance or shared decision-making). It recognises that these may confound the outcomes to be discussed, but also that the quality of healthcare team/patient interactions cannot be measured in a standardised way.

1.3. Hypothesis and aims of the thesis

The introduction has demonstrated that asthma is a heterogeneous condition with 'treatable traits' which are not only pathophysiological but behavioural in nature. Whilst adherence has been clearly demonstrated to be one such trait, there is a paucity of evidence demonstrating that adherence interventions result in better clinical outcomes. Using the emerging gold-standard measure of electronic monitoring, this thesis will assess the performance of EMDs as adherence measures in asthma. It will also assess whether incorporating them into interventions targeting poor adherence results in improved adherence and clinical outcomes in asthma and whether this can be translated into real world settings for clinical use.

Aims

1. **To review the available evidence on electronically monitored adherence in asthma, using it to estimate a population ICS adherence rate in asthma.**

There have been many attempts to assess adherence to asthma therapies. With EMDs mooted as the new gold-standard, *Chapter 2* of this thesis reviews EMD studies, examining

precisely what these devices have been used to measure and how. In doing so, this thesis suggests considerations for the sorts of devices which should be used in future studies and how such use should be reported. *Chapter 2* goes on to use the results of these studies to estimate a population adherence to ICS in asthma, examining the nature of these studies and the potential pitfalls of relying on them to reflect real-world adherence.

2. **To review existing evidence on whether adherence interventions incorporating EMDs lead to better outcomes in asthma.**

By conducting a systematic review with a more limited scope, *Chapter 3* considers the effectiveness of interventions which use EMDs to increase ICS adherence in individuals with asthma, assessing whether success in improving adherence translates into improved clinical outcomes. Limitations of these studies are used as a foundation for methodological recommendations for future research in this area.

3. **To assess the validity of Smartinhaler™ devices in a trial setting.**

Smartinhaler™ (Adherium) devices are a brand of EMDs which have been commonly used and previously validated in the

literature. *Chapter 4* summarises these validation studies. It then goes on to report the results of validation testing of these EMDs conducted as part of a pilot study, comparing the results to published data and considering the implications for real-world use.

4. **To evaluate whether using EMDs as part of an adherence intervention improves outcomes in asthma.**

At the centre of this work, *Chapter 5* presents a pilot study which assesses whether clinician feedback, informed by EMD-derived adherence data, leads to improvements in adherence and clinical outcomes in asthma. It also describes the challenges of designing a study with real-world applicability.

5. **To understand user perspectives on using Smartinhaler™ technology.**

Pilot study participants were invited to describe their experiences of asthma, their treatment and study participation with the aim of developing an understanding of how these factors interacted with their unique experiences of using an EMD. *Chapter 6* of this thesis presents findings from these interviews with implications for future EMD design, study design and real world application.

Chapter 2: Deriving a population adherence from electronic monitoring devices: A systematic review

2.1. Introduction

There are a broad range of estimates for adherence to inhaled corticosteroids (ICS), suggesting disparities in what is being measured, how it is being measured and who it is being measured in. This has the potential to handicap the coherent development of intervention design and construction of a body of evidence. Consequently, there is a need to identify where these disparities lie and how they may affect the evidence already in existence. Doing this would allow such factors to be considered in the development of new interventions.

Adherence can been measured using subjective measures such as retrospective interviews, paper or electronic diaries, clinician estimates and validated questionnaires such as the Morisky Medication Adherence Scale (MMAS) or the Medication Adherence Report Scale for Asthma (MARS-A) (89, 90, 105). Questionnaires in particular have been shown to discriminate between good and poor adherence (90, 106). Despite this, subjective measures can suffer from a 'social desirability' bias,

driven by an individual's desire not to be judged and resulting in under-reporting of non-adherence (105, 107, 108). Retrospective tools are also open to recall bias. Finally, all subjective measures are also open to manipulation by individuals who knowingly under- or over-report their ICS use.

Increasingly, pharmacy records are being used to measure inhaler use to assess whether an individual is eligible for escalation of therapy (34). Prescription refills are routinely recorded in most healthcare data systems, allowing for a widely available estimation of adherence based on how often a prescribed medication is collected. In research, various calculations also attempt to account for irregular usage (105), however, prescription fills do not equate to usage and, by averaging adherence over time, fail to detect some patterns of poor adherence (51).

Many ICS inhalers now incorporate dose counters. These can serve to remind an individual that a dose has been taken or that they require a new prescription. They can also inform investigators or clinicians that the inhaler is being actuated. Dose counters also fail to measure inhaler use patterns and inhalation. Underuse/overuse cycles, critical inhaler errors and dose dumping may therefore go undetected.

Direct measures such as blood prednisolone and cortisol assays do not have a useful equivalent for ICS. Directly observed therapy (DOTs) measures would be organisationally complex, time-consuming and expensive to deliver in an adult setting (46, 109, 110).

Other methods used in the clinical trial setting include weighing canisters and electronic monitoring (51, 111). Fractional exhaled nitric oxide (F_ENO) levels have more recently been investigated as a means of distinguishing between lack of response to therapy and poor adherence (112). Each of these methods have limitations. Older generation EMDs share with both prescription data and canister weighing the inability to detect actual inhalation. Finally, F_ENO measurements in and of themselves are not specific to asthma/ICS adherence and so require a degree of skill to interpret and have generally been used in combination with electronic monitoring (112).

The ideal measure of inhaler use would accurately detect inhaler actuations, assess quality of technique, measure how much drug is deposited in the airways and perhaps even assess how effective the dose has been with minimal invasiveness, discomfort or effort to the user. It would produce a clinically meaningful output not requiring great expenditure of time or skill for the user and clinical team to interpret. Such an ideal

measure does not yet exist. Electronic monitoring, however, is rapidly bridging the gap between the ideal and current methods of monitoring.

In their ubiquitous form, electronic monitors detect, record and time-stamp inhaler actuations. Some devices go further, incorporating means of detecting inhalation and quantifying technique (74, 113). Thus, not only do electronic monitors have the potential to inform as to whether an individual has taken their medication, but also to provide objective, real-time information as to patterns and quality of inhaler use.

This review examines studies where ICS adherence has been electronically monitored. It employs a working definition of adherence being the actuations recorded as a proportion of expected inhaler use. In light of the emerging role of electronic monitoring devices (EMDs) as the gold standard for adherence monitoring in ICS (6), this review asks what is meant by the term EMD and what they measure when they are reported as measuring adherence. The review goes on to offer an estimate of population adherence using electronic measurement alone.

2.2. Objectives

1) To describe electronic monitoring methods for assessing adherence to inhaled corticosteroid therapy in adult asthma used in the literature in terms of:
    1. What is being measured
    2. How it is being measured
    3. How effectively it is being measured
2) To determine the rate of ICS adherence described in the literature using electronically monitored adherence.

2.3. Methods

2.3.1. Protocol

This chapter is drawn from a larger planned work aiming to look at adherence measurement across the spectrum of methods. The protocol for this is included in *Appendix 2* and is registered on the *"Prospero"* database,

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=57708

Searches

Searches were conducted in April 2017. Studies were identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE group of databases, EMBASE, Web of

Science, SCOPUS, CINAHL, PsychINFO and IEEE Xplore. Grey literature searches were conducted using clinicaltrials.gov, BioMedCentral ISRCTN Registry and OpenGrey. Search terms were constructed with advice from the University of Nottingham Library services. The search terms deployed are shown below in *Figure 2-1*.

Figure 2-1: Systematic review search terms

1. exp Asthma/ OR Asthma*.mp.
2. (exp Nebulizers and Vaporizers/) OR (exp Asthma/dt) OR Inhal* OR Aerosol* OR Nebuli*

1. AND
2. (exp Patient Compliance/) OR Adher* OR Complian* OR Co?operat* OR Concord* OR Non?adher* OR Non?complian* OR Non?concord* OR Under?complian* OR Over?complian* OR Monitor*

- OR -

3. EMD OR Smartinhaler OR SmartTrack OR SmartTouch OR Nebulizer Chrono* OR Doser* OR Propeller OR MDILog OR Canister weigh* OR Prescription count* OR Refill count* OR Dose count*

Terms were designed to capture electronic monitoring of ICS from its inception through to the present day and terms reflected the changes in terminology since their first report in the early 1980s. Search terms also reflect the fact that this review forms the initial part of a planned broader study of different methods of adherence monitoring.

2.3.2. Data management

Titles and abstracts were managed using the Covidence online system (www.covidence.org, © 2017 Covidence, Melbourne).

Full texts were managed using EndNote X8 (Clarivate Analytics). Data extraction was conducted in Microsoft Excel (2016). Once checked, data were then imported into Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

2.3.3. Study eligibility

Eligibility criteria were set *a priori*. Studies included randomised controlled trials (RCTs), quasi-experimental studies and cohort studies. This was in recognition of the fact that adherence, particularly in earlier studies, was studied as part of broader interventions. Included study populations were pre-defined as adults having asthma of any severity. The review was limited to studies targeting adults as behavioural factors and management are known to differ over the lifespan. During the course of the review, several key adult studies were identified that included adolescents aged 12-18. The decision was taken to include these studies.

Due to the breadth of the review, the protocol was amended such that studies were required to specify the use of electronic monitors for ICS rather than both ICS and short-acting beta agonists (SABA). Comparators were permitted to include other objective methods of assessing adherence, subjective methods of assessing adherence or no assessment of adherence at all.

Outcomes of accuracy of methods of assessing adherence, change in self-management behaviours or change in clinical outcomes were of interest but not essential.

2.3.4. Study selection

Study selection at both the title and abstract stage was conducted by two independent reviewers. Disagreements were resolved by consensus. Initial screening of full texts was conducted by a single reviewer, however where it was felt that there was a possibility full texts might meet inclusion criteria, two independent reviewers again performed study selection with disagreements resolved either by consensus or by discussion with a third reviewer. Peer-reviewed publications were included in place of abstracts where the abstract had been included prior to article publication. Abstracts and full texts that were not in English were inspected using Google Translate. Any that were judged eligible for inclusion were to be referred for data extraction by someone fluent in that language.

2.3.5. Data extraction

Extraction was performed by two reviewers. Disagreements were resolved by consensus. Where consensus could not be found, disagreements were referred to a third reviewer. A third reviewer checked 10% of the studies included for validation purposes.

Data were extracted onto pre-designed forms. These were tested for usability and then further updated as the study progressed. The variables assessed included general study information, extraction of aspects of study design, how study samples were powered and how large the samples were, description of the study population, description of the devices and their characteristics, adherence and study quality. These forms are included below with shaded cells containing variables added during the course of the review.

Table 2-1: Study information and design

Fields	**Options (*description in italics*)**
Study ID	[First author surname][Year]
Reviewer	*Reviewer initials*
First author	
Year	
Study title	
Journal	
Paper type	Research article, letter, conference abstract, other
Adherence measure	EMD
Multicentre	Yes, no, unknown, n/a
Setting – country	
Meets inclusion criteria	Yes, no
Comments	*For notes on study eligibility*
Setting – care sector	Community (pharmacy or primary care), *[dedicated]* research centres, secondary/specialist care, mixed primary and secondary/specialist, n/a, not reported. *Note this referred to where the study was conducted, not where participants were recruited from* per se*.*
Duration (weeks)	
Study design	RCT, cohort
Study objectives/ endpoint	
Role of adherence	Risk factor, outcome, outcome and risk factor, quality measure
Inclusion criteria	
Exclusion criteria	
Comments	

Table 2-2: Power calculations and sampling

Fields	Options (*description in italics*)
Adherence powered	Yes, no, unclear – *the authors indicate a power calculation to see an adherence outcome effect*
Effect size - adherence	*The adherence effect size being powered for*
Sample size – adherence	*The target sample size resulting from this*
Clinical outcomes powered	Yes, no, unclear - *the authors indicate a power calculation to see an effect on clinical outcomes*
Outcome measure (units)	*E.g. peak flow (L/min)*
Effect size - outcome 1	*The clinical outcomes effect size being powered for*
Sample size - outcome 1	*The resultant target sample size*
Effect size - outcome 2	*Effect size for a second clinical outcome*
Sample size - outcome 2	*The resultant target sample size*
Alpha	
Power	
Approached	*The number of people the authors specify as having been approached to participate*
Eligible	*The number of people the authors specify as having been eligible to participate in the study*
Recruited: Overall Intervention Control	*The number of people the authors specify as having consented to be in the study overall and in the intervention and control groups*
Randomised: Overall Intervention Control	*The number of people the authors specify as having been randomised overall and in the intervention and control groups*
Completed: Overall Intervention Control	*The number of people the authors specify as having completed the study overall and in the intervention and control groups*
Analysed: Overall Intervention Control	*The number of people the authors specify as including in the analysis overall and in the intervention and control groups*
Patients lost to follow-up/withdrawn/ incomplete data	Described - nil of note *(loss to follow-up was >5% but those lost to follow-up did not differ significantly from the group who completed)* Described - issues to note *(loss to follow-up was >5% and those lost to follow-up differed significantly from the group who completed)* Attrition <5% *(loss to follow-up was <5%)*, not Described but intention to treat/whole population

Fields	Options (*description in italics)*
	analysis *(loss to follow-up was not reported but there is evidence of an intention-to-treat analysis)* Not described *(loss to follow-up was not described)*
Comments on loss to follow-up	

Table 2-3: Baseline characteristics

Fields	Options *(description in italics)*
Mean age (years): **Overall (SD)** **Intervention (SD)** **Control (SD)**	*For the overall study population and for each group where available with standard deviations*
Sex (% female)	*The proportion of the study was reported to be female*
Ethnicity considered	Yes, no – *baseline ethnicity data reported*
Population: white	*Proportion of population reported as white/Caucasian etc.*
Population: Afro-Caribbean	*Proportion of population reported as black/black African/African American etc.*
Socio-economic status considered	Yes, no – *baseline socioeconomic data reported*
Did not graduate high school	*Proportion – educational attainment used as the most frequently occurring and standardised surrogate of socioeconomic status (SES)*
Only graduated high school	*Proportion – educational attainment used as the most frequently occurring and standardised surrogate of SES*
Completed further or higher education	*Proportion – educational attainment used as the most frequently occurring and standardised surrogate of SES*
Proportion exacerbation in the last year at baseline	Low (0-33%), medium (34-66%), high (67-100%), other, unreported – *Proportion of population with an exacerbation in preceding twelve months (oral corticosteroid use, unscheduled GP* visits for asthma, ED† visits for asthma, hospitalisations for asthma). "Other" modes of reporting exacerbations included lifetime or rates.*
Proportion ED or hospital admission in the last year at baseline	Low (0-15%), medium (16-30%), high (>30%), other, unreported
Baseline FEV_1‡ measured	Yes, no
Mean FEV_1% predicted (SD)	*Population mean FEV_1 percentage predicted and standard deviation*

Fields	**Options** *(description in italics)*
Pre-study ICS dose (SD)	*Reported mean baseline ICS dose and standard deviation*
Study ICS	*The ICS supplied during the study if standardised and reported*
Study ICS dose	*The dose of ICS supplied during the study if standardised and reported*
Baseline reliever use measured	Yes, no – *the authors report a measure of reliever use at baseline*
Validated subjective asthma control measured	Yes, no – *the authors report a validated measure of asthma control such as (but not limited to) ACT™§, ACQ¶, AQLQ# at baseline*
Mean ACT™ (SD)	*Mean baseline population asthma control test score (standard deviation)*
Mean ACQ7 (SD)	*Mean baseline population asthma control questionnaire score (standard deviation)*
Other subjective asthma control measured	Yes, no – *a study-constructed measure of asthma control with no previous external validation is reported by the authors*
Baseline differences	Yes, no, unclear, n/a – *reported baseline differences between groups*
Comment on represented population	

** General Practice/General Practitioner (GP)*
† Emergency Department (ED)
‡ Forced expiratory volume in 1 second (FEV_1)
§ Asthma Control Test™ (ACT™)
¶ Asthma Control Questionnaire (ACQ)
 # Asthma Quality of Life Questionnaire (AQLQ)

Table 2-4: Devices

Fields	**Options** *(description in italics)*
Name	*Device name*
Structure	*How the authors describe the device's structure e.g. attached to the inhaler*
Date stamp	*The authors report device date stamps actuations**
Time stamp	*The authors report device time stamps actuations**
Detects inhalation	*The authors report device detects inhalation*
Assesses inhalation	*The authors report device can assess the quality of inhalation/technique*
Study period analysed (weeks)	*The duration over which EMD-collected data were analysed*
Adherence measure	Actuations, days, actuations and days, proportion, other – *the reported adherence outcome measure included for use. Actuations usually reported as mean actuations taken as a proportion of actuations prescribed. Days usually reported as mean percentage days ICS taken correctly as a proportion of study days. Proportion usually the*

Fields	**Options *(description in italics)***
	percentage of the study population meeting a pre-specified adherence cut-off.
Adherence vs Non-adherence	Adherence, non-adherence – *results primarily reported in terms of adherence or in terms of non-adherence*
Equation	*How electronically monitored adherence is calculated including the time period over which it is calculated (usually 12hrs or 24hrs then averaged out over the study period)*
Adherence summary statistic	Mean, median, other, not reported
Was adherence capped?	Yes, no – *the authors' report on whether adherence was truncated to mitigate the effect of inappropriate overuse, usually capped at 100%*
Cap limit	
Validity comment	Previously validated, commercially available, validation study, not validated, mixed, no comment on validity – *author comments on previous validation of the EMD(s) used*
Device accuracy	*Authors' comments on device accuracy*
Failure rate	*Proportion of EMD that malfunctioned during the course of the study*
Comparator (non-EMD) adherence	*e.g. subjective, dose counter, canister weight*
Comments on device strengths/ weaknesses	*Have the authors commented on what they feel the particular strengths/limitations of their device(s) may be?*
Comments - other	

**Date/time stamps initially extracted as a combined variable and then separated over the course of the review*

Table 2-5: Results

Fields	**Options *(description in italics)***
Baseline adherence (%): Overall (SD/IQR) Intervention (SD/IQR) Control (SD/IQR)	*Pre-intervention adherence overall and per group (summary statistic and measure of spread)*
Overall raw adherence (%) (SD)	*Whole population adherence, usually reported over whole study period. This unadjusted value may be reported separately to a "true" adherence value.*
Overall finalised adherence (%) (SD)	*Whole population adjusted adherence e.g. capped to exclude overuse or accounting for inhaler technique.*
Intervention adherence (%) (SD)	*Adjusted (if available) adherence for RCT intervention group over the measured study period.*

Fields	Options *(description in italics)*
Control adherence (%) (SD)	*Adjusted (if available) adherence for RCT control group over the measured study period.*
p-value/CI	*Reported p-value or confidence interval for any significant change in adherence*
Adherence cut-off (%)	*Pre-specified cut-off to characterise "good" adherence*
Proportion of population reported adherent (%)	*Proportion of study population reported as having met cut-off for "good" adherence*
Adherence decay (%): **Overall** **Intervention** **Control**	*The difference between baseline or peak adherence and adherence at the end of the study.*
Overuse	*Overuse of ICS is reported – yes, no*
Comparator (non-EMD) adherence measure	None, canister weight, prescription record, dose counter, other objective, subjective, unclear - *any other adherence measures used – space only for a second measure*
Comparator adherence (SD)	*Adherence reported as measured by objective comparator method*
Improved clinical outcomes	Yes, no – *where clinical outcomes e.g. exacerbations/quality of life/FEV_1 were reported, did the study demonstrate a statistically significant change related to a change in adherence?*
Comments	

2.3.6. Outcome measures

1. Primary outcome: a population estimate of electronically monitored adherence.
2. Secondary outcomes:
    a. A narrative synthesis of how the literature defines electronically monitored adherence
    b. Characteristics of devices used to measure adherence
    c. Reported EMD accuracy
    d. Comparison of electronically monitored adherence between intervention and control groups.

e. Comparison of electronically monitored adherence with other objective modes of adherence measurement

For the purpose of the meta-analysis, adherence has been calculated as the proportion of expected inhaler puffs which were electronically recorded as actuated. The narrative synthesis details specifics of how this was done from study reports.

2.3.7. Quality Assessment

Risk of bias was assessed and reported descriptively by adapting the Cochrane Collaboration's tool for RCTs (114) which examines five domains. Risk of selection bias was judged by reporting of random sequence generation and allocation concealment in RCTs. In the version adapted by this review for cohort studies, it looked for evidence of representative sampling. Performance bias assessed blinding of participants and personnel. This was adapted to incorporate blinding to EMD purpose and function. Detection bias looked for outcome assessment blinding. Attrition bias looked at the completeness of outcome data and extent of missing data. Finally, for RCTs, reporting bias looked for selective outcome reporting. The final score was out of seven for both RCTs and cohort studies. The

terms used and their definitions are included in *Tables 2-6* and *2-7* below.

Table 2-6: Risk of bias (RCTs)

Fields	Options	Description
Random sequence generation	Low – 1 Unclear – u High – 0	How randomisation was performed.
Allocation concealment	Low – 1 Unclear – u High – 0	Whether allocation was reported as concealed and if so, how.
Participant and personnel blinding/ effectiveness	Double/ low - 1 Single/ intermediate – 0.5 Unblinded/high – 0 Unclear – u	Procedures reported for blinding participants and for blinding personnel to participant group.
Blinding to EMD/function	Double/ low – 1 Single/ intermediate – 0.5 Unblinded/high – 0 Unclear – u	Procedures reported for blinding participants to EMD function and personnel collecting data to EMD results.
Outcome assessment blinding	Low – 1 Unclear – u High – 0	Procedures reported for blinding study analysis.
Incomplete outcome data	Low – 1 Unclear – u High – 0	Description of loss to follow-up and missing data.
Selective outcome reporting…	Low – 1 Unclear – u High – 0	To what degree analysis was by intention to treat (ITT). If clear reason for ITT modification and <=5% participants excluded, a low risk score was considered.

Table 2-7: Risk of bias (cohort studies)

Fields	Options	Description
Representative sampling	Low – 2 Intermediate - 1 Unclear – u High – 0	E.g. if the study was for a general asthma population, did the study recruit from the community? Have exclusion criteria been minimised? Were patients who did not enter the study markedly different to the sample population?

Fields	Options	Description
Participant and personnel blinding/ effectiveness	Low – 1 Unclear - u High – 0	Procedures reported for blinding participants and for blinding personnel to participant group.
Blinding to EMD/function	Double/ low - 1 Single/ intermediate – 0.5 Unblinded/ high – 0 Unclear – u	Procedures reported for blinding participants to EMD function and personnel collecting data to EMD results.
Outcome assessment blinding	Low – 1 Unclear - u High – 0	Procedures reported for blinding study analysis.
Incomplete outcome data	Very low – 2 Low – 1 Unclear – u High – 0	Description of loss to follow-up and missing data. If <=5% loss, score as very low risk. If 5-15% loss and differences to remaining sample reported score as low risk. If 5-15% loss and differences to remaining sample not reported, score as low risk with an unreported element which may contribute to bias. If >15% loss, score as high risk. Specify "unclear" if unreported information may influence risk of bias.

2.3.8. Data synthesis

Narrative synthesis

As not all review objectives and all studies could be included in a meta-analysis, a narrative synthesis is provided. This presents the following measures of adherence outcomes by study:

1. Baseline adherence (%)
2. Overall adherence (%)
3. Adherence by group (%)
4. p-values for RCTs where available

5. Change (decline) in adherence from study start to study end both overall and by group (%)
6. Proportion of the study population deemed adherent (%)

Separately described are the following:

1. The studies themselves
2. Study sampling (including numbers of participants recruited, randomised and analysed)
3. Population characteristics (including age, sex, ethnicity and asthma control)
4. Devices (including capabilities such as ability to date/time stamp and detect inhalation)
5. How adherence is measured from study to study (including duration of data analysed, whether or not adherence was capped and whether or not overuse was reported).

Finally, a narrative synthesis of the effect of RCT interventions on clinical outcomes is provided as this could not be examined by meta-analysis due to the disparate outcome measures.

Meta-analysis – inclusion

A meta-analysis of adherence at baseline, over the course of the study and compared between intervention and control

groups is also presented. Studies were included in the meta-analysis as follows:

1. Adequate summary data could be derived directly from the study report, or
2. Adequate study data was provided such that summary data was calculable, or
3. A reasonable estimate from available data could be made (e.g. where participant numbers analysed were not clearly reported, the number of participants who either completed the study or were randomised to the study were used to estimate this).

For the meta-analysis, a random effects model was used, in expectation that there would be variation in the outcome measures due to study variations. The I^2 statistic is also presented, acknowledging potential variations in population, in the types and capabilities of EMDs used, and in how adherence was defined and measured from study to study.

Meta-analysis – adherence

Population adherence estimates were obtained using two methods:

1. Pooling baseline adherence in studies where this was available.

2. Pooling end of study adherence from cohort study populations and RCT control groups.

An estimate of the effect of interventions on adherence was obtained from RCTs which could be included in the meta-analysis. Individual study means and standard deviations (SD) were combined to give a standardised mean difference (SMD) and 95% confidence intervals. The SMD provides a pooled measure of effect which denotes a magnitude of effect from 0-1.0. An SMD of 0.2 denotes a small effect size, 0.5 a moderate effect size and 0.8 a large effect size (115, 116). This allows for comparison of effect between disparate adherence measures. For reference, a mean difference in percentage adherence with 95% confidence intervals has also been presented.

Subgroup analyses were conducted to assess whether ethnicity, socioeconomic status and asthma severity had an effect on study-period adherence. To assess whether ethnicity proportions in studies had an effect on adherence, studies were split into binary groups based on whether they had a proportion ≥50% of white participants. Similarly, studies reporting educational attainment were divided into studies reporting ≥25% of participants not graduating high school and studies reporting <25% participants not having graduated high school. Difficult asthma was ascertained using two measures. First, a

percentage predicted forced expiratory volume in one second (FEV_1) of <80% was used as this suggests evidence of a fixed airflow obstruction, a known marker of risk in asthma (6, 21). Secondly, asthma control scores signifying lack of control i.e. Asthma Control Test™ [ACT™]<20 and Asthma Control Questionnaire [ACQ]>1.5 were used as these are often used as a benchmark for inclusion in clinical studies (21).

Meta-analysis – comparator measures

An estimate of the difference between study adherence obtained using EMDs and study adherence using other objective measures of adherence was derived. This meta-analysis again utilised the SMD as varying comparator methods were used by different studies.

Meta-analysis – study quality and sensitivity

Finally, studies were categorised into binary high- and low-quality study groups, split by the median risk of bias score. Further analyses permitting no more than one area with an unclear risk of bias and separately not permitting any areas consistent with a high or unclear risk of bias were also undertaken. Sensitivity analysis was conducted to assess the impact of study quality on estimates of population adherence.

2.4. Results

Figure 2-2 provides the PRISMA flow diagram for this systematic review (117). Thirty-four papers were identified for analysis in this initial electronic monitoring sub-study (54, 56, 60, 67, 68, 74, 88, 90, 99-101, 118-140).

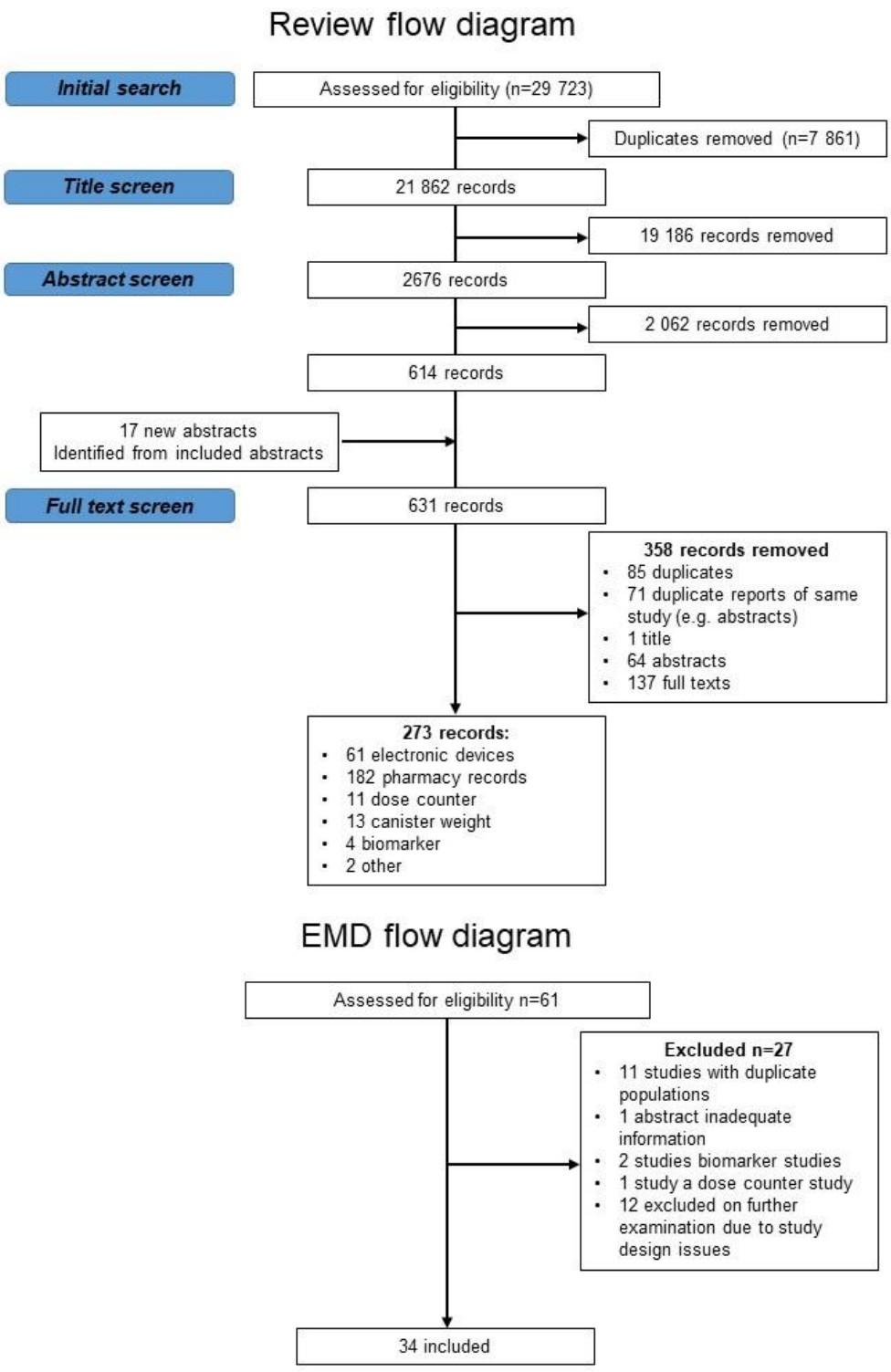
2.4.1. Description of studies

General

Due to the broad nature of this review, several papers are included which did not report data in the mode required for meta-analysis, but were still considered to be of narrative value (74, 88, 90, 100, 101, 119, 121, 123, 125, 126, 131, 132, 134, 137, 139, 141). Where studies incorporated populations also reported elsewhere (e.g. D'Arcy et al., (142)), relevant findings from these auxiliary reports were incorporated into the narrative review.

Studies were published between 1991 and 2019 in the United States (19 of the 34 papers), United Kingdom (UK), Australia, New Zealand, Republic of Ireland, Canada, Spain and The Netherlands *(see Table 2-8)*. In one of these papers, two separate studies were reported (138). These are analysed separately (i.e. 35 studies from 34 papers). Of the 35 studies, 18 were cohort studies and 17 RCTs.

Figure 2-2: Systematic review flow diagram



Thirteen studies were reported as multicentre and, of 25 studies reporting setting, 18 were conducted solely in research or specialist centres, signifying a smaller body of evidence directly generalizable to primary care. Study duration ranged from 2 – 56 weeks, with a median duration of 10 weeks (interquartile range 6 – 24 weeks).

Study designs varied considerably. Of the 18 cohort studies, 16 were purely observational and two assessed study groups who had undergone a self-management intervention (136, 139). RCTs also varied with two studies which used ICS adherence as a quality rather than an outcome measure (101, 131) and studies which did consider it to be an outcome testing different categories of interventions. Some of these included behavioural interventions such as the use of audio-visual reminders (AVR) and feedback (67, 68, 99, 100, 118, 120, 121, 124-126, 141). Others tested drug regimes including dosing frequency and combination inhalers (122, 129, 133, 135).

Management of control groups also differed between studies. Some control groups were reported as receiving usual care (100, 125), others received educational interventions (99, 118), or, due to how the study groups had been structured, a mixture of usual care and a behavioural intervention (68).

Others received new inhalers, free inhalers or were reimbursed for the cost of their inhalers (67, 100, 118).

Sampling and population

Across the 35 studies, a total of 3478 participants were recruited, ranging from studies with ten participants to a study with 339 participants recruited. One thousand three-hundred and ninety-three of these participants were from cohort studies, whilst over half (n=2085) were from RCTs. Five studies were powered for adherence *(see Table 2-8)* and three for clinical outcomes (101, 132, 134).

Table 2-8: A systematic review of electronically monitored adherence: Study information

Study ID	Country	Sample powered for adherence	Recruited Overall	Randomised - Intervention	Randomised - Control	Analysed Overall	Analysed - Intervention	Analysed - Control	Incomplete data*
Apter1998 (119)	USA		54			50			not described
Apter2003 (56)	USA		88			85			attrition <5%
Apter2011 (118)	USA	330	333	165	168	unclear	unclear	unclear	not described
Bender2010 (120)	USA	50	50	25	25	50	25	25	not described but intention to treat/whole population analysis
Berg1997 (121)	USA		68	31	24	55	31	24	attrition <5%
Bosley1994 (122)	UK		102	51	51	72	36	36	described - issues to note
Charles2007 (67)	New Zealand	100	110	55	55	90	44	46	not described
Chmelik1994 (139)	USA					20			not described
Cluley2001 (88)	UK		103			66			described - issues to note
Cohen2009 (90)	USA		53			53			attrition <5%
D'Arcy2014 (123)	ROI		69			51			not described
Foster2011 (54)	Australia		100			85			not described

Study ID	Country	Sample powered for adherence	Recruited Overall	Randomised - Intervention	Randomised - Control	Analysed Overall	Analysed - Intervention	Analysed - Control	Incomplete data*
Foster2014 (68)	Australia		143	76	67	129	67	62	not described
Goeman2013 (124)	Australia		124	66	58	123	65	58	not described but intention to treat/whole population analysis
Janson2009 (126)	USA	80	95	45	39	84	45	39	described - nil of note
Janson2010 (125)	USA	136	139	68	71	139	68	71	not described but intention to treat/whole population analysis
Krishnan2004 (127)	USA		60			49			described - issues to note
Lacasse2005 (128)	Canada	125	134			124			not described
Le2008 (60)	USA		86			86			attrition <5%
Mann1992_a (129)	USA		17			16	8	8	described - issues to note
Mann1992_b (130)	USA		10			10			attrition <5%

Study ID	Country	Sample powered for adherence	Recruited Overall	Randomised - Intervention	Randomised - Control	Analysed Overall	Analysed - Intervention	Analysed - Control	Incomplete data*
Mawhinney1991 (131)	USA		15	7	8	15	7	8	attrition <5%
McGann2008 (132)	USA		51			48			attrition <5%
Onyirimba2003 (100)	USA		30			19	10	9	described - nil of note
Patel2013_c (101)	New Zealand		303	151	152	303	151	152	not described but intention to treat/whole population analysis
Perrin2010 (133)	New Zealand	100	111	57	54	103	54	49	not described
Plaza2016 (134)	Spain		99			99			attrition <5%
Rand2007 (135)	USA		177	189	191	169			
Sulaiman2016_b (74)	ROI					82			not described
Sulaiman2018 (99)	ROI	200	218	111	107	206	105	101	not described
vanderPalen1997 (136)	The Netherlands		24			21			not described
Weinstein2019 (141)	USA		50	27	23	39	19	20	not described

Study ID	Country	Sample powered for adherence	Recruited Overall	Randomised - Intervention	Randomised - Control	Analysed Overall	Analysed - Intervention	Analysed - Control	Incomplete data*
Wells2016 (137)	USA					339			attrition <5%
Yeung1994_s1 (138)	UK		10			10			not described
Yeung1994_s2 (138)	UK		11			11			not described

**Lost to follow-up/withdrawn/otherwise incomplete data*

Study mean/median ages ranged from 32.0 – 67.7 years (*Table 2-9*). Studies reported between 26.7% to 85.0% female participants. Race and socioeconomic circumstances were only intermittently reported, with only seventeen studies reporting a measure of ethnicity and sixteen a measure of socioeconomic circumstances using a variety of measures and making comparison between studies challenging. *Table 2-9* presents the most commonly used and easily comparable measures – percentage of the participant population reported to be of white or Afro-Caribbean ethnicity and the percentage of the participant population who did not graduate from high school.

Eight studies reported exacerbations (defined as systemic steroid use or unscheduled service visits), ED attendances and/or hospitalisations in the preceding 12 months rates *(see Table 2-9)*. Some studies reported these figures in other ways, for example mean hospital admission rates per person. Nineteen studies reported participant FEV_1 at baseline and 20 studies reported baseline subjective asthma control using a validated scoring system. Only five studies reported baseline reliever use.

Table 2-9: A systematic review of electronically monitored adherence: Baseline characteristics

Study ID	Mean age	Sex (% female)	Ethnicity (% white)	Ethnicity (% Afro-Caribbean)	Did not graduate high school	Exacerbation rate*	ED / hospital admission rate†	Mean FEV_1 % predicted	Mean ACT™	Mean ACQ7
Apter1998 (119)	46.0	74.0	42.0	22.0	32.0			75.0		
Apter2003 (56)	47.0	72.0		65.0				65.0		
Apter2011 (118)	49.0	72.0	20.0	68.0	17.0	medium	high	66.0		1.7
Bender2010 (120)	41.6	64.0	58.0	20.0						
Berg1997 (121)	50.0	66.0	95.0		2.0					
Bosley1994 (122)	44.0	61.0						73.5		
Charles2007‡ (67)		54.6								
Chmelik1994 (139)	39.8	75.0				medium	high			
Cluley2001 (88)	41.9	66.0								
Cohen2009 (90)	47.0	85.0	6.0	31.0	43.0					
D'Arcy2014 (123)	46.8	56.5								
Foster2011 (54)	47.6	58.0						82.8	19.9	
Foster2014 (68)	40.3	62.0				low		77.1	14.6	
Goeman2013 (124)	67.7	72.4			2.4	low		73.7		1.4
Janson2009 (126)	38.2	53.6		6.0				80.8		
Janson2010 (125)	50.0	68.4				low	low	81.3		
Krishnan2004 (127)	42.2	65.0	1.7	98.3			high			
Lacasse2005 (128)	47.0	58.9						78.0		1.8
Le2008 (60)	42.7	69.8	23.3	70.9	41.0					
Mann1992_a (129)	44.6	81.3								
Mann1992_b (130)	43.8	80.0								

Study ID	Mean age	Sex (% female)	Ethnicity (% white)	Ethnicity (% Afro-Caribbean)	Did not graduate high school	Exacerbation rate*	ED / hospital admission rate†	Mean FEV_1 % predicted	Mean ACT™	Mean ACQ7
Mawhinney1991 (131)	32.5	26.7								
McGann2008 (132)	42.0	82.4	78.4					77.0		
Onyirimba2003 (100)	48.8	84.2			53.0			70.9		
Patel2013_c (101)	42.0	69.0	76.2			high		81.0		1.9
Perrin2010 (133)	47.3	55.0						81.1		1.3
Plaza2016 (134)	47.8	67.7			28.3			79.6		
Rand2007 (135)	35.2	69.5	80.8					93.9		
Sulaiman2016_b (74)	54.8	59.0			42.0					
Sulaiman2018 (99)	49.2	64.0				high		73.0	12.1	
vanderPalen1997 (136)	42.0	47.6								
Weinstein2019 (141)	40.0	60.7						72.8		2.3
Wells2016 (137)	33.7	58.4	28.6	71.4				72.9	18.6	
Yeung1994_s1 (138)	38.0	40.0								
Yeung1994_s2 (138)	32.0	72.7								

** Proportions grouped as low (≤33%), medium (33-66%) or high (>66%) use of oral/systemic steroids in preceding 12 months for asthma exacerbation*
† Proportions grouped as low (≤15%), medium (15-30%) or high (>30%) ED attendance and/or hospital admission for asthma exacerbation
‡ Ages given as medians for each group, no overall summary statistic

2.4.2. Devices

Nine device brands were reported by studies in this review. These were the Doser (including the Doser Clinical Trials version, Doser CT), the INCA device, the MDI Chronolog, the MDI Log, the Nebulizer Chronolog, the Smartinhaler™, the Turbuhaler Inhalation Computer (TIC), the Diskus Adherence Logger (DAL) and the Electronic Diskhaler *(see Table 2-10)*. The studies by Yeung et al. published an unbranded *"electromechanical counter"*. Three studies used a mixture of devices.

There was variable reporting of how the EMD interacted with the inhaler *(Table 2-10)*. Thirteen studies reported their EMD was attached to the inhaler, six that a standard metered dose inhaler (MDI) canister was inserted into the EMD and one that the EMD was integrated into the device, another specifying a concealed microchip. Of the studies using more than one device brand, one specified that one of the devices was a canister sleeve and two specified that their devices attached to the inhalers.

Twenty-five studies clearly reported that the EMD(s) used provided a date stamp for actuations, 26 that they provided a time stamp for actuations, five that they detected inhalation and four that the EMD system was able to evaluate inhalation

technique *(Table 2-10)*. Fourteen studies reported that at least one of the device models used was either previously validated and/or commercially available. Three were validation studies.

The remaining 32 studies did not report any validation data *(Table 2-10)*. Fifteen studies gave no report of device accuracy during the study period *(see Table 2-10)*. Where device failure rates were reported (12 studies), the median failure rate was 12.5% devices (interquartile range 7.6 – 15.2%). For the two brands in current use in the literature – the Smartinhaler™ and the INCA – reported failure rates were 12-13% and 6.5-9.81% respectively.

Table 2-10: A systematic review of electronically monitored adherence: Description of devices

Study ID	Name(s)	Structure	Date stamp	Time stamp	Detects inhalation	Assesses inhalation quality	Validity comment	Failure rate (%)
Apter1998 (119)	MDI Chronolog	canister sleeve	yes	yes	not reported	not reported	no comment on validity	
Apter2003 (56)	MDILog	not reported	yes	yes	not reported	not reported	no comment on validity	
Apter2011 (118)	Diskus Adherence Logger; MDILog	attached	yes	yes	not reported	not reported	mixed	20.0
Bender2010 (120)	MDILog; Doser CT; Diskus Adherence Monitor [Logger]	attachment	not reported	not reported	not reported	not reported	previously validated	
Berg1997 (121)	MDI Chronolog	houses MDI	yes	yes	not reported	not reported	previously validated	1.0
Bosley1994 (122)	Turbuhaler Inhalation Computer	integrated	yes	yes	yes	yes	no comment on validity	35.0
Charles2007 (67)	Smartinhaler™	canister sleeve	yes	yes	not reported	not reported	no comment on validity	
Chmelik1994 (139)	Nebulizer Chronolog	unclear	yes	yes	not reported	not reported	no comment on validity	
Cluley2001 (88)	No info	concealed microchip	yes	yes	not reported	not reported	no comment on validity	
Cohen2009 (90)	MDI-Log	attached	not reported	not reported	not reported	not reported	no comment on validity	
D'Arcy2014 (123)	INCA	attached	not reported	yes	yes	yes	validation study	9.8

Study ID	Name(s)	Structure	Date stamp	Time stamp	Detects inhalation	Assesses inhalation quality	Validity comment	Failure rate (%)
Foster2011 (54)	Smartinhaler™	not reported	yes	yes	not reported	not reported	no comment on validity	13.0
Foster2014 (68)	Smartinhaler™ (SmartTrack)	attached	yes	yes	not reported	not reported	previously validated	
Goeman2013 (124)	Smartinhaler™		not reported	yes	not reported	not reported	no comment on validity	
Janson2009 (126)	Doser CT	attached	yes	not reported	not reported	not reported	previously validated	
Janson2010 (125)	Doser CT	not specified	not reported	not reported	not reported	not reported	no comment on validity	
Krishnan2004 (127)	Doser CT	not specified	yes	not reported	not reported	not reported	previously validated	
Lacasse2005 (128)	MDILog II	accept a metered-dose inhaler mouthpiece and canister	yes	yes	not reported	not reported	previously validated	7.5
Le2008 (60)	MDILog	not specified	yes	yes	not reported	not reported	no comment on validity	
Mann1992_a (129)	Nebulizer Chronolog	canister sleeve	yes	yes	not reported	not reported	no comment on validity	
Mann1992_b (130)	Nebulizer Chronolog	canister sleeve	yes	yes	not reported	not reported	commercially available	

Study ID	Name(s)	Structure	Date stamp	Time stamp	Detects inhalation	Assesses inhalation quality	Validity comment	Failure rate (%)
Mawhinney1991 (131)	Nebulizer Chronolog		yes	yes	not reported	not reported	no comment on validity	
McGann2008 (132)	Doser		unclear	not reported	not reported	not reported	previously validated	15.7
Onyirimba2003 (100)	MDI Chronolog	canister sleeve	yes	yes	not reported	not reported	no comment on validity	
Patel2013_c (101)	Smartinhaler™	*"incorporated into all …MDIs dispensed"*	yes	yes	not reported	not reported	previously validated	
Perrin2010 (133)	Smartinhaler™	canister sleeve	yes	yes	not reported	not reported	previously validated	
Plaza2016 (134)	Smartinhaler™	attached	yes	yes	not reported	not reported	no comment on validity	
Rand2007 (135)	MDILog	not specified	yes	yes	unclear	unclear	previously validated	14.7
Sulaiman2016_b (74)	INCA	attached	yes	yes	yes	yes	previously validated	6.5
Sulaiman2018 (99)	INCA	attached	not reported	yes	yes	yes	previously validated	7.8
vanderPalen1997 (136)	Nebulizer Chronolog; Electronic Diskhaler	canister sleeve (NC) Not specified (ED)	yes	yes	yes	no	no comment on validity	13.6
Weinstein2019 (141)	SmartTrack	attached	yes	yes	not reported	not reported	no comment on validity	12.0

Study ID	Name(s)	Structure	Date stamp	Time stamp	Detects inhalation	Assesses inhalation quality	Validity comment	Failure rate (%)
Wells2016 (137)	Doser CT	attached	not reported	unclear	not reported	not reported	no comment on validity	
Yeung1994_s1 (138)	electromechanical counter	attached	no	no	not reported	not reported	validation study	
Yeung1994_s2 (138)	electromechanical counter	attached	no	no	not reported	not reported	validation study	

2.4.3. Defining adherence

At its most rudimentary, adherence was calculated over the whole study period. Some studies excluded data periods which were at risk of dose dumping. Some divided data into dosing periods (most commonly 24 hours) and calculated a daily adherence which was then averaged over the study period *(see Table 2-11)*. To further limit the influence of dose dumping or periods of overuse masking periods of underuse, half of the 34 studies reviewed placed a cap (usually 100% of expected doses) on adherence. Eighteen studies reported ICS overuse.

Several studies used EMDs with technique-measuring capabilities. Some of these studies integrated technique into their adherence measurement, sometimes giving this figure alongside time-based adherence. Various studies used levels between 50-90% to define "good" adherence. From this, the studies divided their populations into adherent and non-adherent groups *(see Table 2-11)*.

Table 2-11: A systematic review of electronically monitored adherence: Definitions of adherence by study

Study ID	Study duration (weeks)	Study period analysed (weeks)	Primary adherence definition	Dosing period	Adherence cap limit per dosing period	Minimum dosing gap	Adherence summary statistic	Overuse reported	Primary adherence cut-off (%)
Apter1998 (119)	6	5	recorded actuations/ prescribed actuations	12 hrs	100% + 4 actuations		mean	yes	70
Apter2003 (56)	6	6	recorded actuations/ prescribed actuations	12 hrs	100%		mean	yes	
Apter2011 (118)	24	24	recorded actuations/ prescribed actuations	24 hrs	100%		mean	no	
Bender2010 (120)	10	10	recorded actuations/ prescribed actuations	10 weeks			mean	no	
Berg1997 (121)	6*	8			100%		median	no	80
Bosley1994 (122)	12	12	recorded actuations/ prescribed actuations	12 weeks			mean	yes	80
Charles2007 (67)	24	12	recorded actuations/ prescribed actuations	final 12 weeks	100%	6 hrs	mean/median	yes	
Chmelik1994 (139)	5	1	recorded actuations/ protocol-defined actuations		110%		other	yes	90
Cluley2001 (88)	8	8	recorded actuations/ prescribed actuations	8 weeks				no	70
Cohen2009† (90)	12	4	percentage days ≥1 actuation/30 days	24 hrs	3.5 hours + unclear	3.5 hrs	mean	no	70

Study ID	Study duration (weeks)	Study period analysed (weeks)	Primary adherence definition	Dosing period	Adherence cap limit per dosing period	Minimum dosing gap	Adherence summary statistic	Overuse reported	Primary adherence cut-off (%)
D'Arcy2014 (123)	12	12	cumulative number of correctly taken doses plotted against cumulative number of prescribed doses; slope compared to regression line of perfect adherence	7 days			not reported	no	
Foster2011 (54)	8	7	recorded actuations/ prescribed actuations	24 hrs	100%		mean	no	
Foster2014 (68)	24	24	recorded actuations/ prescribed actuations				mean	no	
Goeman2013 (124)	48	6	recorded actuations/ prescribed actuations	12 hrs			mean	no	80
Janson2009 (126)	24	18	recorded actuations/ prescribed actuations	1 week	100% / 24hrs		mean	no	60
Janson2010 (125)	52	52	recorded actuations/ prescribed actuations	1 month	100%		mean	no	
Krishnan2004 (127)	2	2	recorded actuations/ prescribed actuations		100%		mean	no	50
Lacasse2005‡ (128)	12	12	recorded actuations/ prescribed actuations	24 hrs	100%		mean	yes	75
Le2008 (60)	4	4	recorded actuations/ prescribed actuations	4 weeks	100% / 24 hrs		mean/median	no	

Study ID	Study duration (weeks)	Study period analysed (weeks)	Primary adherence definition	Dosing period	Adherence cap limit per dosing period	Minimum dosing gap	Adherence summary statistic	Overuse reported	Primary adherence cut-off (%)
Mann1992_a (129)	6	6	percentage days in study period actuations recorded were not equal to 8	24 hrs	12 actuations		mean	yes	
Mann1992_b (130)	9	9	recorded actuations/ prescribed actuations	24 hrs			mean	yes	100
Mawhinney1991 (131)	4	4	days 8 actuations / total days	24 hrs			mean	yes	75 (days)
McGann2008 (132)	56	1.71	days prescribed number of actuations recorded/ 12 days	24 hrs	no cap		mean	yes	80
Onyirimba2003 (100)	10	10	recorded actuations/ prescribed actuations	1 week	100%		mean	yes	
Patel2013_c (101)	24	24	proportion ≥0 actuation days/total number of days 0 actuations	24 weeks			mean	yes	
Perrin2010 (133)	24	24	recorded actuations/ prescribed actuations	final 6 weeks		6 hrs[§]	mean	yes	80
Plaza2016 (134)	2	2	correctly taken actuations/ prescribed actuations		100%		mean	no	80
Rand2007 (135)	48	36	recorded actuations/ prescribed actuations per subject averaged across subjects	24 hrs		3 hrs[§]	mean	yes	

Study ID	Study duration (weeks)	Study period analysed (weeks)	Primary adherence definition	Dosing period	Adherence cap limit per dosing period	Minimum dosing gap	Adherence summary statistic	Overuse reported	Primary adherence cut-off (%)
Sulaiman2016_b (74)	4	4	cumulative drug exposure (area under the curve)	4 weeks			mean		80
Sulaiman2018 (99)	12	12	cumulative drug exposure (area under the curve) incorporating both critical errors in technique and missed doses	final 4 weeks			mean	yes	80
vanderPalen1997 (136)	6	6	recorded actuations/ prescribed actuations				mean	yes	75
Weinstein2019 (141)	12	12	recorded actuations/ prescribed actuations	24 hrs	100		mean	no	60
Wells2016 (137)	6	6	recorded actuations/ prescribed actuations	24 hrs			mean	unreported	
Yeung1994_s1 (138)	2	2	recorded actuations/ prescribed actuations				mean	yes	70
Yeung1994_s2 (138)	3	3	recorded actuations/ prescribed actuations				mean	yes	70

** Duration of intervention rather than measurement*
† Common definition of adherence (i.e. recorded actuations/ prescribed actuations) used as a secondary definition
‡ First and last days excluded from analysis
§ Not used in primary measure of adherence

This review showed studies still used arbitrary thresholds of adherence to report sample proportions who had good adherence. These were, however, generally reported alongside summary measures of individual dose adherence. Finally, some studies used measures which precluded their comparison with other studies (101).

2.4.4. Narrative adherence

Adherence for each study (including those which could not be included in the meta-analysis) is presented in *Table 2-12*. Where the primary definition of adherence was not the proportion of actuations prescribed recorded as taken but this was calculated, the latter is presented. Also presented is change in adherence over the study period (reported by 14 studies) and the proportion of study population adherent.

Control groups ranged from improvements in adherence over the study period of 7.2% to declines of 11%. Intervention groups ranged from an improvement in adherence of 19.3% to a decline of 13.8%. Where reported overall, change in adherence over the study period ranged from an improvement of 4% to a decline of 37.8%.

Table 2-12: A systematic review of electronically monitored adherence: Population adherence

Study ID	Baseline adherence (%)	Overall end adherence (%)	Standard deviation	Adherence decline - overall (%)	Intervention adherence (%)	Adherence decline - intervention (%)	Control adherence (%)	Adherence decline - control (%)	p-value	Proportion adherent* (%)
Apter1998 (119)				8.0						54.0
Apter2003 (56)		60.0	30							
Apter2011 (118)	61.0	53.5	28.5		55.0	10.0	52.0	14.0		
Bender2010 (120)		56.8	18.3		64.5		49.1		0.003	
Berg1997 (121)					46.0	-6.0	23.0	11.0	0.043	16.4
Bosley1994 (122)		63.5	33.6		67.0		60.0			14.5
Charles2007 (67)		76.8	24.8		88.0		66.0			
Chmelik1994 (139)										40.0
Cluley2001 (88)										53.0
Cohen2009 (90)		35.0								
D'Arcy2014 (123)				-4.0						
Foster2011 (54)		75.0	25.0	13.0						
Foster2014 (68)		60.0	30.1		73.0		46.0		<0.001	
Goeman2013 (124)	69.6				89.3	-19.3	76.4	-7.2		
Janson2009 (126)	81.5				77.0	5.0	73.0	7.0		
Janson2010 (125)									0.160	
Krishnan2004 (127)		55.9	30.8	37.8						59.2
Lacasse2005 (128)		72.0	24.0							53.2
Le2008 (60)		34.0	24.0							
Mann1992_a (129)	91.2				84.8	13.8	85.16	-2.5	0.001	
Mann1992_b (130)		67.0	36.0	16.0						

Study ID	Baseline adherence (%)	Overall end adherence (%)	Standard deviation	Adherence decline - overall (%)	Intervention adherence (%)	Adherence decline - intervention (%)	Control adherence (%)	Adherence decline - control (%)	p-value	Proportion adherent* (%)
Mawhinney1991 (131)		87.5								0.0
McGann2008 (132)		36.0								10.4
Onyirimba2003 (100)	56.3					6.0		25.0		
Patel2013_c (101)										
Perrin2010 (133)		78.3	27.7		82.4		73.7			54.4
Plaza2016 (134)										49.5
Rand2007 (135)		63.9	25.9	6.3						
Sulaiman2016_b (74)		61.7								
Sulaiman2018 (99)		68.1	25.4		73.0	-10.0	63.0	4.0	0.010	45.0
vanderPalen1997 (136)	83.0	92.0	52.0							63.0
Weinstein2019 (141)					81.0	12.0				73.7
Wells2016 (137)	79.0									
Yeung1994_s1 (138)		77.6	30.5							80.0
Yeung1994_s2 (138)		69.7	26.7							54.6

**The proportion of each study population which achieved a threshold of ICS adherence pre-defined by each study*

2.4.5. Clinical outcomes

Fourteen RCTs using an adherence-based intervention with EMDs as their measure of adherence investigated clinical outcomes in addition to adherence outcomes. Only four reported an improvement in clinical outcomes. These included statistically significant differences in ACQ (124, 126, 141) as well as night-time awakenings (126), symptoms, oral corticosteroid (OCS) use and unscheduled service use (125).

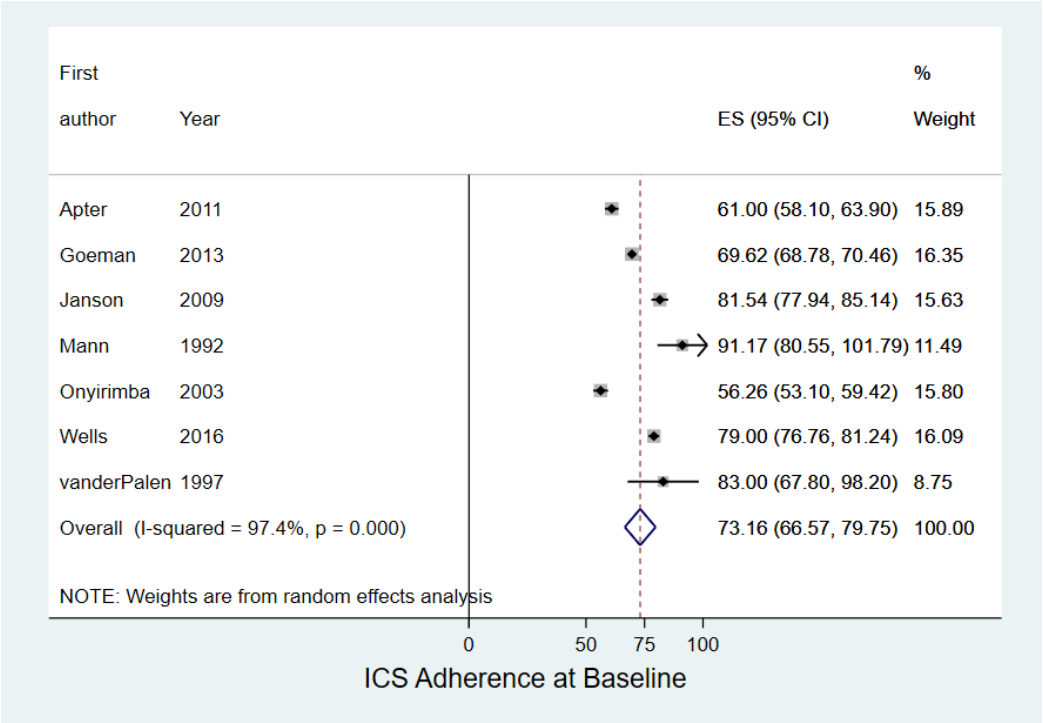
2.4.6. Electronically monitored estimates of population adherence by meta-analysis

Two potential measures of population adherence are presented:

1. Pooled study baseline adherence
2. Pooled cohort and control group adherence

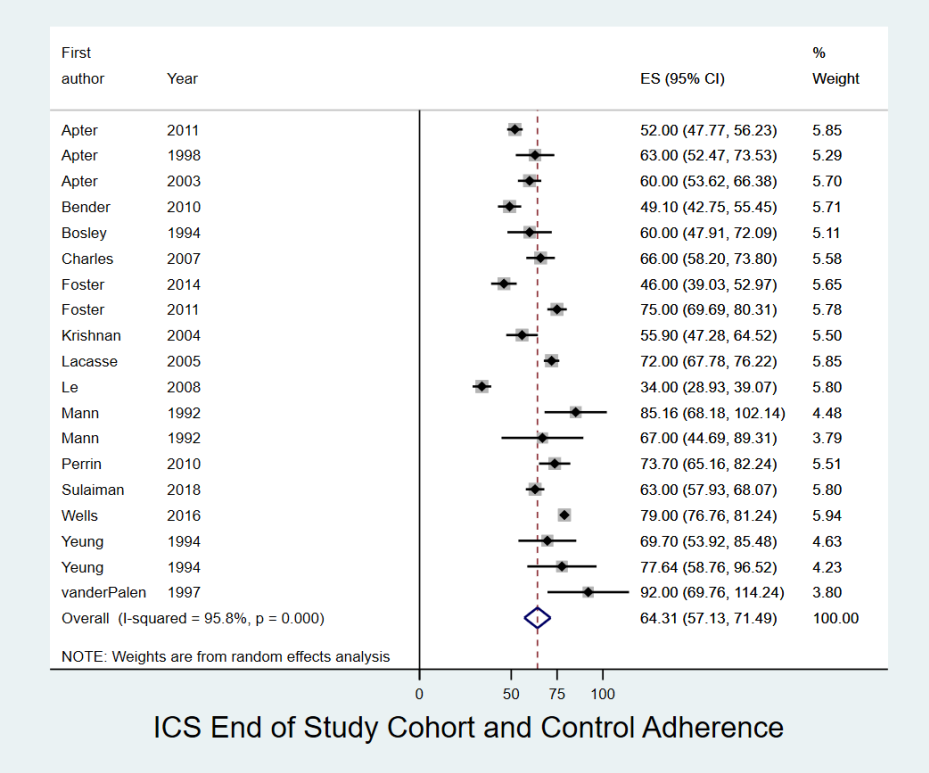
Seven studies representing 962 participants gave a pooled baseline adherence estimate of 73.2% (95% CI 66.6-79.8, I^2 97.4%) as shown in *Figure 2-3*.

Figure 2-3: Meta-analysis of study adherence – estimate of electronically monitored population adherence using study baseline adherence



Combining cohort and control group adherence from 19 studies representing data from 1365 participants gave a pooled estimate of 64.3% (95% CI 57.1-71.5%, I^2 95.8%, see *Figure 2-4*).

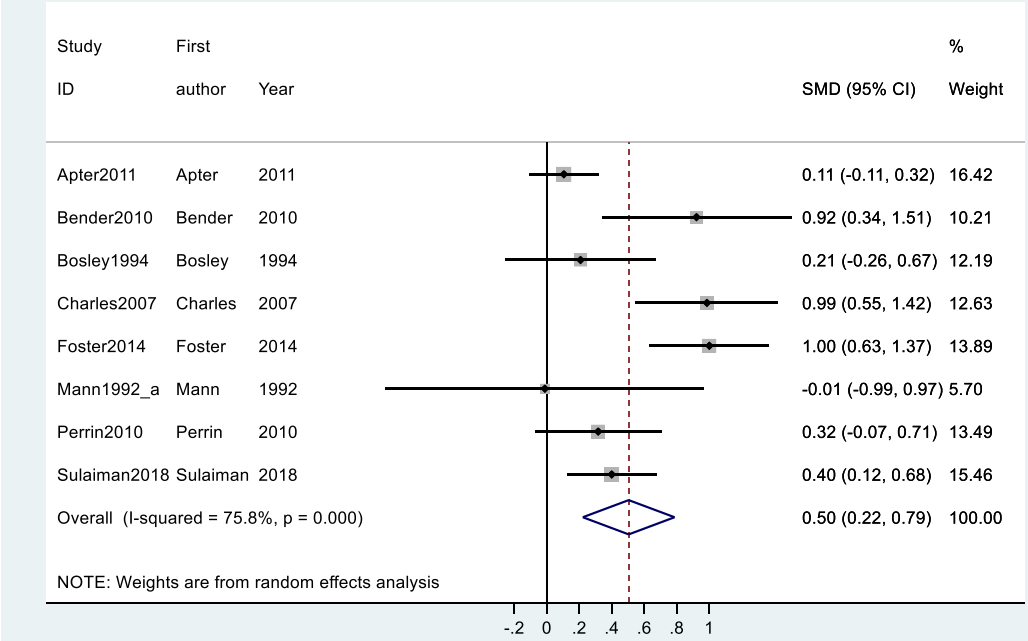
Figure 2-4: Meta-analysis of study adherence – estimate of electronically monitored population adherence using combined cohort and control group adherence



2.4.7. RCTs: treatment effect on adherence

Eight RCTs provided post-intervention between-group differences for meta-analysis. The overall SMD for adherence in intervention vs control groups was 0.5 (95% CI 0.2-0.8, I^2 75.8%), indicating that RCTs saw a moderate improvement in adherence in response to interventions *(*see also *Figure 2-5)*. This represents a weighted mean difference (WMD) of 12.7% (95% CI 6.1 – 19.3%, I^2 72.2%).

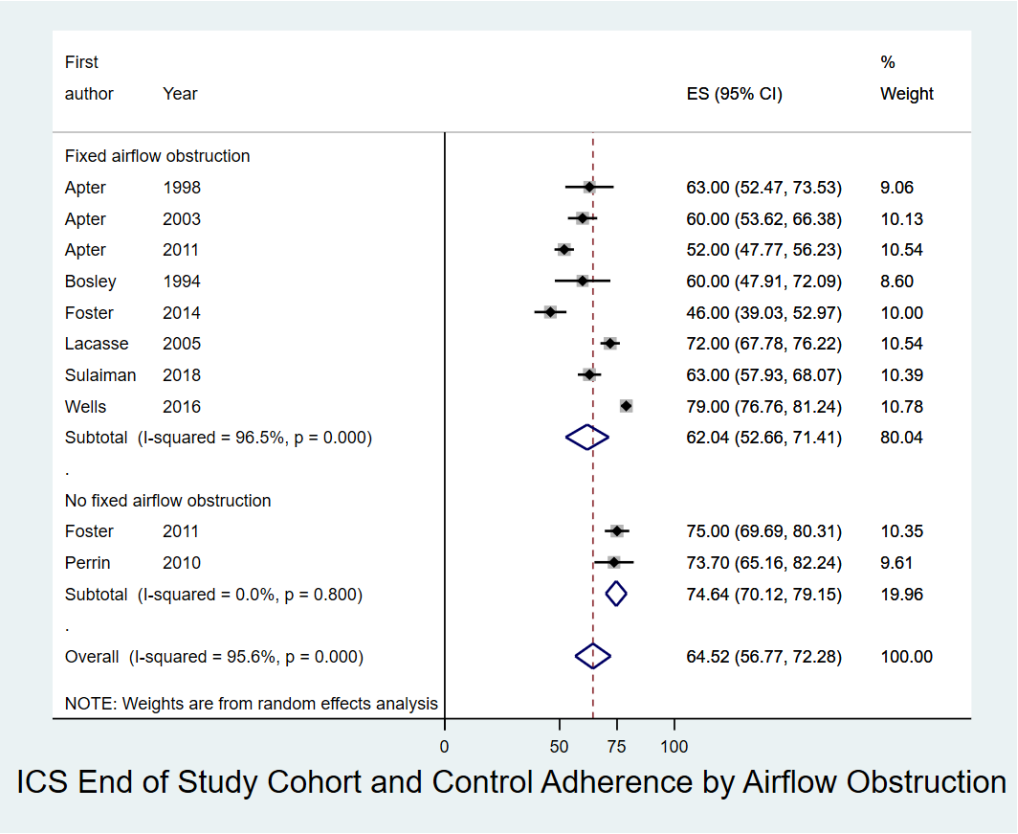
Figure 2-5: Meta-analysis of study adherence – between-group difference in adherence for RCTs



2.4.8. Subgroup analyses

Subgroup analyses looking at the effects of race, socioeconomic status and asthma severity (fixed airflow obstruction and asthma control) found no significant differences in adherence, although there was a signal towards fixed airflow obstruction affect cohort/control group adherence *(Figure 2-6).* It is also noted that only a few studies reported adequate relevant data for each of the subgroups, limiting the scope of the subgroup analyses.

Figure 2-6: Meta-analysis of study adherence - Subgroup analysis by airflow obstruction of cohort and control group adherence



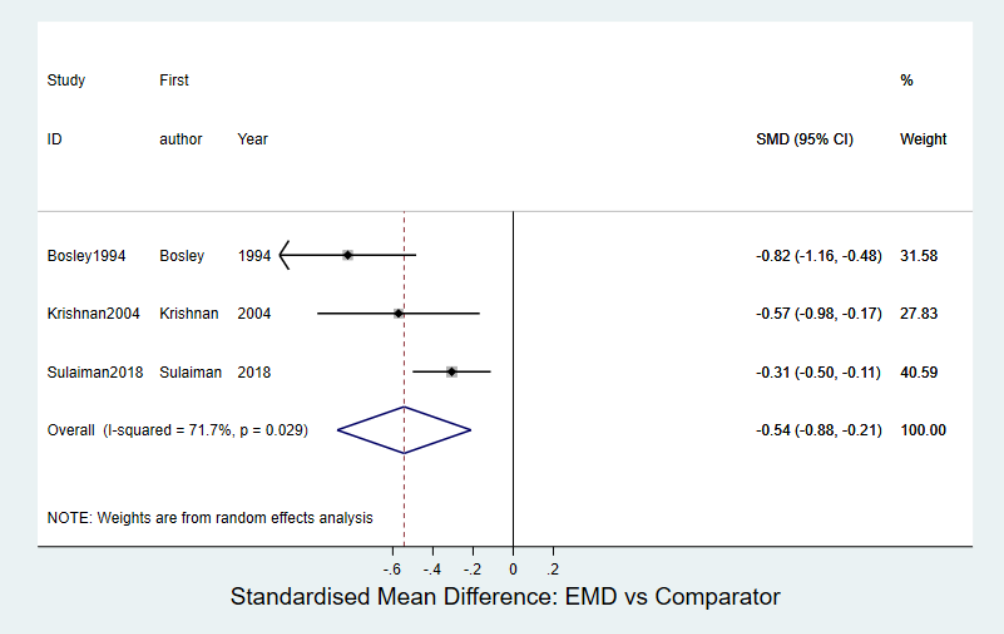
2.4.9. Comparison with other methods of adherence

Only 13 studies reported use of a comparator measure of adherence. Of these, seven reported use of an objective comparator (canister weight and dose counter). One described the comparator (dose counter) as the gold standard (123). This study could not be included in the meta-analysis as there was no measure of variance reported.

Three studies were eligible to be included in this paired analysis (*see Figure 2-7*). EMDs appeared to report a lower level of adherence than other objective methods of adherence

monitoring with an SMD of -0.5 (95% CI -0.9 to -0.2, I^2 71.7%), p=0.029.

Figure 2-7: Meta-analysis of electronically monitored adherence: EMD versus comparator



2.4.10. Study quality and sensitivity analysis

The main challenge across studies was blinding participants and study personnel to interventions where these were behavioural or where the use of an EMD was not covert. Other issues included lack of clarity with regards to whether personnel involved in outcome assessment also had access to EMD data and significant drop-out rates (see *Tables 2-13 and 2-14).*

The median risk of bias score obtained from the modified quality assessment was 2.0 and the median number of unclear domains was two. A status of higher quality/lower risk of bias was therefore assigned to studies achieving a quality score of ≥2.0

with two or fewer unclear domains. Overall, 19 studies (ten cohort and nine RCTs) were judged to be of higher quality/lower risk of bias by this definition (54, 56, 67, 68, 74, 90, 99, 101, 120, 124-128, 130, 133, 134, 138).

With the application of stricter criteria, the number of studies found to be high quality/low risk of bias reduced. Where high quality was defined as the median score of 2.0 with no unclear domains permitted, only four studies of the 35 met this standard (68, 120, 124, 125). Where high quality was defined by having no domains with a high or unclear risk of bias, only one of the 35 studies met this standard (125).

Table 2-13: A systematic review of electronically monitored adherence: Study quality assessment (RCTs)

Study ID	Random sequence generation	Allocation concealment	Participant and personnel blinding/ effectiveness - study	Participant and personnel blinding/ effectiveness - EMD	Outcome assessment blinding	Incomplete outcome data	Selective outcome reporting (ITT vs per protocol)	Quality score - overall quantifiable*	Number of domains unclear*
Apter2011 (118)	low - 1	high - 0	unblinded - 0	unblinded - 0	unclear - u	unclear - u	unclear - u	1.0	3
Bender2010 (120)	low - 1	low - 1	unblinded/high - 0	double-blind - 1	low - 1	low - 1	low - 1	6.0	0
Berg1997 (121)	low - 1	unclear - u	unclear - u	unclear - u	unclear - u	unclear - u	low - 1	2.0	5
Bosley1994 (122)	unclear - u	unclear - u	unblinded - 0	single-blind - 0.5	high - 0	high - 0	high - 0	0.5	2
Charles2007 (67)	low - 1	low - 1	unblinded/high - 0	single-blind - 0.5	unclear - u	high - 0	high - 0	2.5	1
Foster2014 (68)	low - 1	low - 1	unblinded/high - 0	single-blind/intermediate - 0.5	low - 1	high - 0	high - 0	3.5	0
Goeman2013 (124)	low - 1	low - 1	single-blind - 0.5	single-blind/intermediate - 0.5	high - 0	low - 1	low - 1	5.0	0
Janson2009 (126)	low - 1	unclear - u	unblinded/high - 0	single-blind - 0.5	low - 1	low - 1	low - 1	4.5	1
Janson2010 (125)	low - 1	low - 1	double-blind - 1	single-blind/intermediate - 0.5	low - 1	low - 1	low - 1	6.5	0

Study ID	Random sequence generation	Allocation concealment	Participant and personnel blinding/ effectiveness - study	Participant and personnel blinding/ effectiveness - EMD	Outcome assessment blinding	Incomplete outcome data	Selective outcome reporting (ITT vs per protocol)	Quality score - overall quantifiable*	Number of domains unclear*
Mann1992_a (129)	low - 1	unclear - u	unblinded/high - 0	single-blind - 0.5	unclear - u	low - 1	unclear - u	2.5	3
Mawhinney1991 (131)	unclear - u	unclear - u	unblinded/high - 0	unblinded/high - 0	low - 1	unclear - u	unclear - u	1.0	4
Onyirimba2003 (100)	unclear - u	unclear - u	unblinded/high - 0	unclear - u	unclear - u	low - 1	high - 0	1.0	4
Patel2013_c (101)	low - 1	low - 1	unblinded - 0	unclear - u	high - 0	low - 1	low - 1	4.0	1
Perrin2010 (133)	low - 1	low - 1	unblinded/high - 0	single-blind - 0.5	unclear - u	low - 1	unclear - u	3.5	1
Rand2007 (135)	low - 1	unclear - u	unblinded/high - 0	unclear - u	unclear - u	high - 0	unclear - u	1.0	4
Sulaiman2018 (99)	low - 1	unclear - u	unblinded - 0	unblinded - 0	unclear - u	high - 0	low - 1	2.0	2
Weinstein2019 (141)	unclear - u	unclear - u	unblinded/high - 0	unblinded/high - 0	high - 0	high - 0	unclear - u	0.0	3

**For the purpose of the meta-analysis, studies were considered high quality with a score of 2.0 or higher and two or fewer unclear domains.*

Table 2-14: A systematic review of electronically monitored adherence: Quality assessment (cohort studies)

Study ID	***Representative sampling***	***Blinding to study***	***Blinding to EMD(s)***	***Outcome assessment blinding***	***Incomplete outcome data***	**Quality score***	**Domains unclear***
Apter1998 (119)	low - 2	low - 1	unclear - u	unclear – u	low - 1 u	4.0	3
Apter2003 (56)	intermediate - 1	low - 1	unclear - u	unclear – u	very low - 2	4.0	2
Chmelik1994 (139)	unclear - u	low - 1	single/intermediate - 0.5	unclear – u	unclear - u	1.5	3
Cluley2001 (88)	high - 0	unclear - u	single blind - 0.5	unclear – u	high - 0	0.5	2
Cohen2009 (90)	intermediate - 1	unclear - u	unblinded/high - 0	unclear – u	very low - 2	3.0	2
D'Arcy2014 (123)	intermediate - 1	high - 0	unblinded - 0	unclear – u	high - 0	1.0	1
Foster2011 (54)	intermediate - 1	low - 1	single blind - 0.5	unclear – u	low - 1 u	3.5	2
Krishnan2004 (127)	low - 2	high - 0	single/intermediate - 0.5	unclear – u	high - 0	2.5	1
Lacasse2005 (128)	intermediate - 1	high - 0	unclear - u	low – 1	low - 1	3.0	1
Le2008 (60)	intermediate - 1	unclear - u	unblinded/high - 0	unclear – u	unclear - u	1.0	3
Mann1992_b (130)	high - 0	low - 1	unclear - u	unclear – u	low - 1	2.0	2
McGann2008 (132)	low - 2	unclear - u	unblinded - 0	unclear – u	unclear - u	2.0	3
Plaza2016 (134)	intermediate - 1	unclear - u	unclear - u	high – 0	very low - 2	3.0	2
Sulaiman2016_b (74)	low - 2	high - 0	unblinded - 0	unclear – u	high - 0	2.0	1
vanderPalen1997 (136)	intermediate - 1	high - 0	unblinded/high - 0	unclear – u	high - 0	1.0	1
Wells2016 (137)	low - 2	unclear - u	unblinded/high - 0	unclear – u	unclear - u	2.0	3
Yeung1994_s1 (138)	high - 0	unclear - u	unblinded/high - 0	unclear – u	very low - 2	2.0	2
Yeung1994_s2 (138)	high - 0	unclear - u	single/intermediate - 0.5	unclear – u	very low - 2	2.5	2

**For the purpose of the meta-analysis, studies were considered high quality with a score of 2.0 or higher and two or fewer unclear domains.*

Using the first definition of study quality where study quality was differentiated by median score/unclear domains, sensitivity analysis did not demonstrate a statistically significant difference between the overall study findings and findings in higher quality/lower risk of bias studies (*Figures 2-8* and *2-9*) i.e. study quality as defined by the median quality score/number of unclear domains did not significantly affect the findings of this meta-analysis.

Figure 2-8: Meta-analysis of study adherence – sensitivity analysis of baseline electronically monitored adherence by study quality (median score)

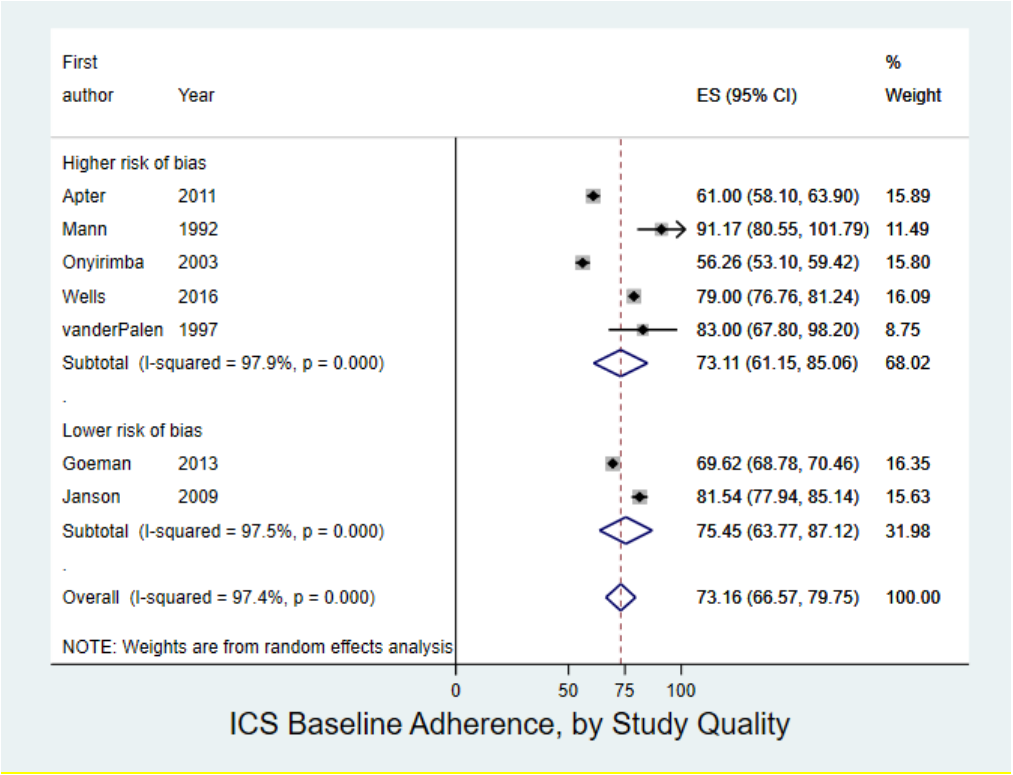
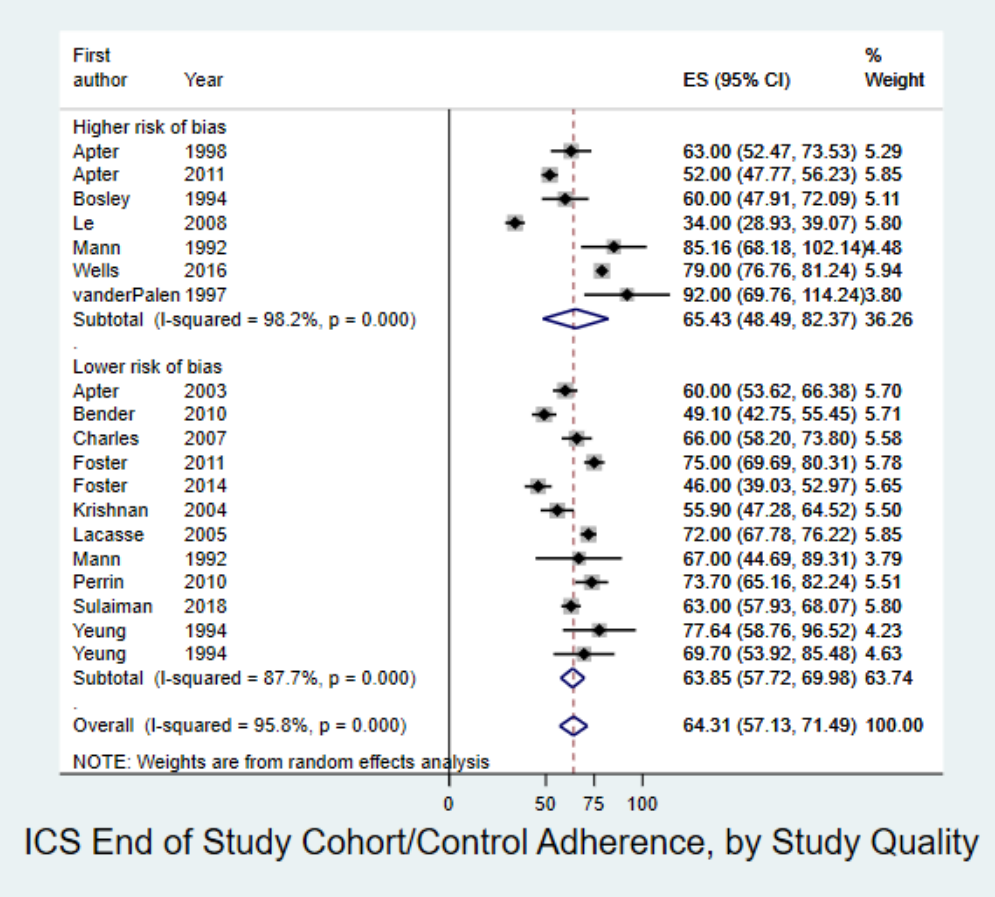


Figure 2-9: Meta-analysis of study adherence – sensitivity analysis of electronically monitored end of study cohort and control group adherence by study quality (median score)



Using the second, more stringent, definition of study quality where no unclear domains were permitted, there remained no effect on a population estimate by baseline adherence (*Figure 2-10*). It did, however, have a significant effect on the population estimate of adherence by cohort studies/control groups (see *Figure 2-11*). Studies judged to be higher quality/lower risk of bias had a significantly lower adherence rate (47.8%, 95% CI 43.0 – 52.4%, I^2 0.0%) than studies of lower quality/higher risk of bias (66.4%, 95% CI 59.0 – 73.9%, I^2 95.6%) and as compared to the overall estimate (64.3%,

95% CI 57.1 – 71.5%, I^2 95.8%). Furthermore, a signal towards studies of higher quality/lower risk of bias by this definition seeing a greater interventional study effect (SMD) when compared with lower quality/higher risk of bias studies was observed (*Figure 2-12*).

Figure 2-10: Meta-analysis of study adherence – sensitivity analysis of baseline electronically monitored adherence by study quality (no unclear domains)

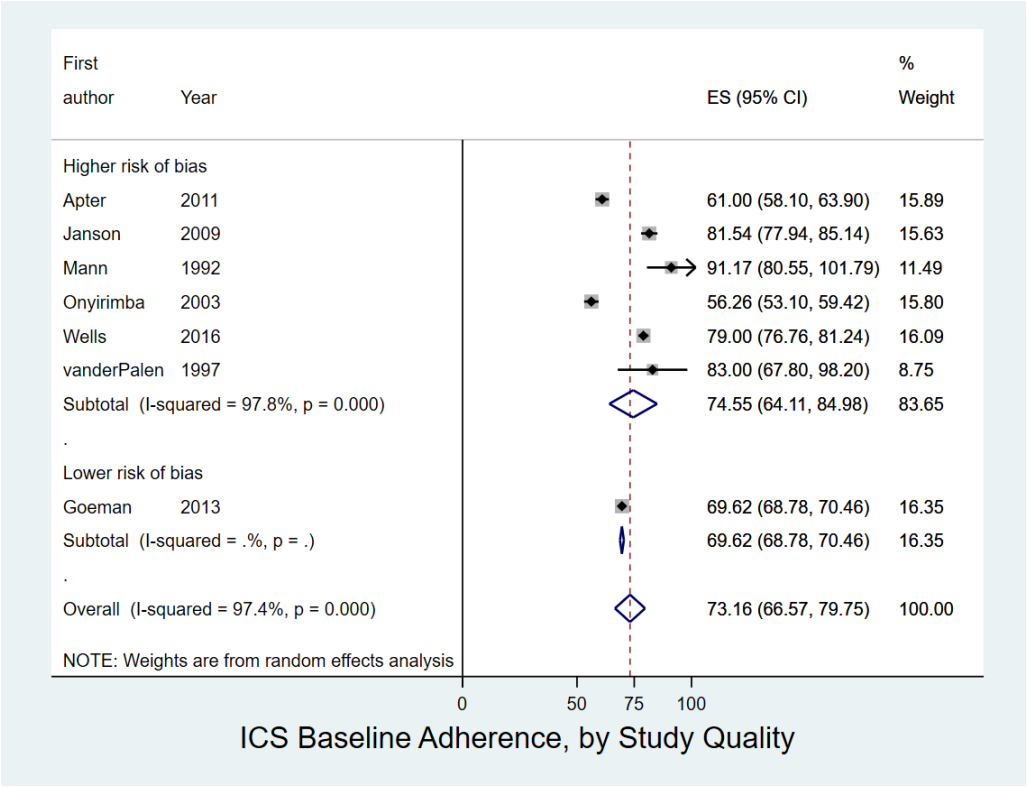


Figure 2-11: Meta-analysis of study adherence – sensitivity analysis of electronically monitored end of study cohort and control group adherence by study quality (no unclear domains)

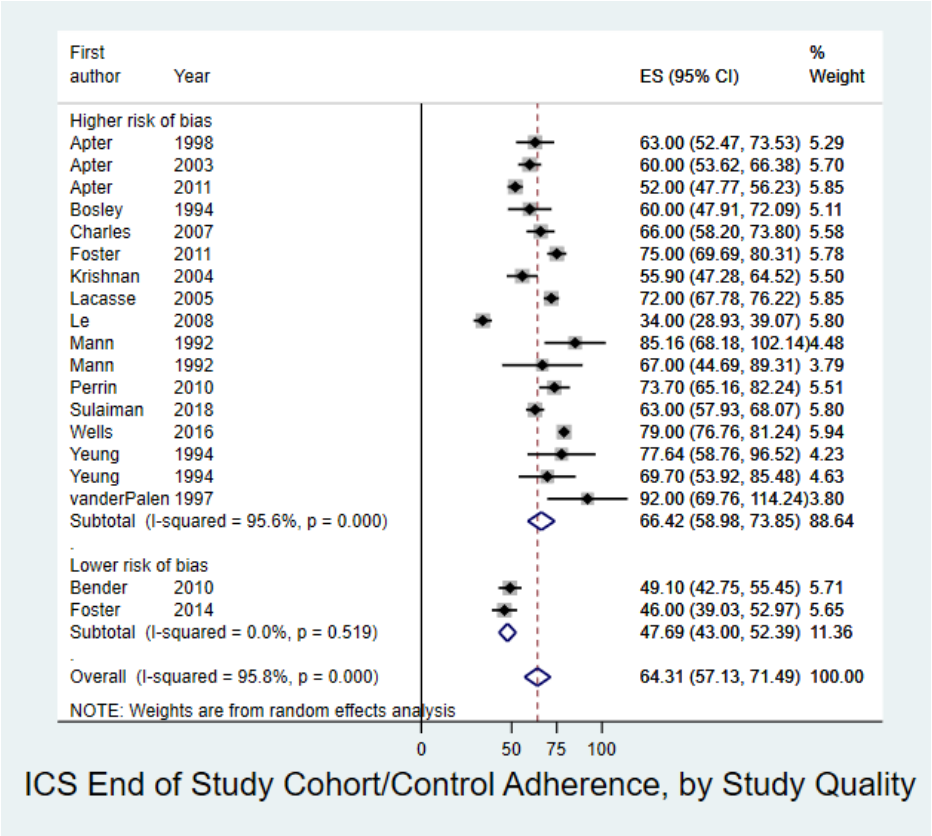
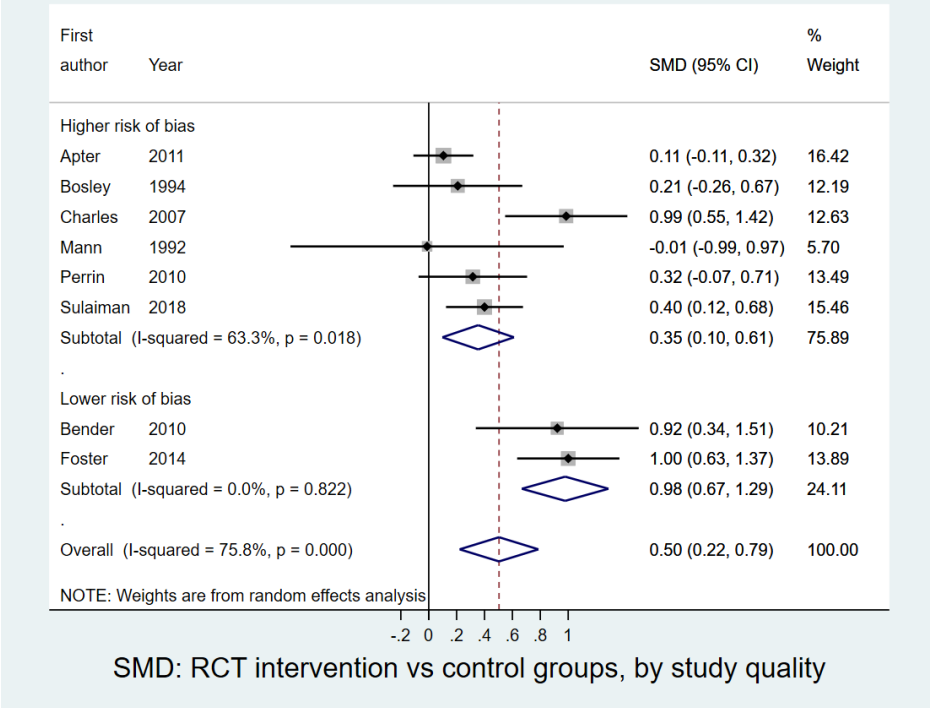


Figure 2-12: Meta-analysis of study adherence – sensitivity analysis of the SMD in interventional studies by study quality (no unclear domains)



2.5. Discussion

2.5.1. Overall study findings

This review found 35 studies in 34 papers using EMDs to measure ICS adherence in a population of 3478 adults published up to and including 2017. Estimates of population adherence were drawn from a baseline adherence of 73.2% and cohort/control group adherence of 64.3%.

Moderate EMD effectiveness in improving adherence behaviours was suggested by a weighted mean difference of 12.7% between intervention and control groups. That this led to an improvement in clinical outcomes was less clear, with only four out of fourteen studies reporting clinical benefit.

2.5.2. How studies define and measure adherence

As electronically measured adherence emerges as the gold standard of adherence monitoring, clarity of what is meant by adherence and how it is measured is required. The prime selling point of EMDs over alternative measures of adherence is their ability to remotely report detailed patterns of inhaler use, not just estimates of canister emptying. This review demonstrated important differences between the devices used in different studies which go beyond branding. On one end of the spectrum,

some devices which did not measure a date and/or time stamp were labelled as EMDs. On the opposite end of the spectrum were devices which incorporated not only a date and time stamp but also an assessment of inhalation quality. In order to provide adequate differentiation from other objective forms of adherence measurement, the presence of both a date and a time stamp should be minimum requirements for an EMD. This should be an important consideration in interpreting existing evidence and in selecting EMDs going forwards, both for research and for clinical practice.

This review demonstrates a range of accuracies across devices and charts the emergence and fall from favour of various brands. Some of the more commonly used brands exhibited device failures. The possibility that as many as 10% of participants may have inaccurate results as a result of device malfunction is a matter for concern explored further in *Chapter 4*. As new devices emerge onto the market, rigorous independent validation data must be a pre-requisite for clinical use. Furthermore, studies should be encouraged to reference device validation data as a marker of quality. This review suggests, however, that pre-existing validation data should not lead studies to neglect reporting in-study device accuracy. For comparison across the literature, device malfunctions should be

reported as a proportion of devices which failed after having been issued. Some of these failures may be minor and may not affect data integrity but should be reported regardless.

In reviewing the evidence in adherence measurement, this review noted that the widely used surrogate marker of doses actuated as a proportion of doses prescribed neither indicates dose delivery nor effectiveness. Higher levels of adherence or overuse at specific periods (e.g. when symptomatic or before a study visit) may also mask underuse at other times. Some studies have employed devices capable of detecting drug inhalation and even inhalation technique. Others have adjusted for overuse by separating dosing periods truncating adherence at maximum expected usage. This heterogeneity in how adherence is defined and calculated is not new, but should be taken into account when comparing outcome measures (46).

Ideal definitions of adherence are limited by device capabilities. There is as yet no available evidence that more complex measures are more clinically meaningful, although this would intuitively be the case. Until such evidence emerges, however, simple measures of temporal adherence which acknowledge patterns of overuse (accounting for windows of reduced airways anti-inflammatory cover) are likely to be adequate.

2.5.3. An EMD-derived estimate of population adherence in asthma

Two estimates of population adherence were presented. Baseline adherence, being "pre-intervention", should have provided the most accurate estimate of real-world population adherence. However, measured at the end of short run-in periods, the novelty of study participation and physical changes in inhaler device may have rendered it particularly susceptible to observer (Hawthorne) effect (143).

An estimate based on combined control/cohort groups provided a larger sample, however this estimate will also have been limited by Hawthorne effect. Further limitations to this estimate result from intrinsic study design differences. As already discussed, some cohort studies included behaviour-changing processes (e.g. assessment of a self-management programme (136)) and some control groups received interventions over and above usual care (68, 99)).

Both estimates are higher than previous estimates, particularly considering that most previous estimates are based on non-EMD data (non-EMD data has consistently been shown to result in higher adherence estimates than EMD data (107, 108)). This may be explained by the requirement of study enrolment for provision of EMDs in both the RCTs and cohort studies included. Such a requirement sets these studies apart from, for example,

managed care database studies, which do not require active participation. Consequently participants are not aware that they are being observed and do not alter their behaviour. Not only does this mean EMD measures are susceptible to Hawthorne effect, they also share risks of selection bias as individuals with poor adherence may be less motivated to enrol or complete studies. Patchy reporting of race/ethnicity, socioeconomic status and baseline asthma control (see *Table 2-9*) may further limit their applicability to known at-risk populations.

That the processes of trial enrolment and participation themselves likely impact on adherence is supported by the literature. Compliance in clinical trials of ICS from the 2000s tended to be reported at rates of over 80%, including when measured objectively (144, 145). This was in stark contrast with cross-sectional survey data from the same period, where even self-reported levels of good adherence (i.e. daily or as prescribed ICS use) ran as low as 27% (146-148). Similarly retrospective claims data showed that, in patients who persisted with therapy, adherence rates could be as low as 50% (33) and ICS persistence as low as 10% (33, 149).

Of interest, sensitivity analysis suggested that studies with a lower risk of bias also provided a lower estimate for the combined cohort/control adherence than overall estimates

(47.8% vs 64.3%) with lower statistical heterogeneity, although this was not the case for baseline adherence (69.6% vs 73.2%). This further supports the argument that electronically monitored baseline adherence measured during a run-in period may be more susceptible to a Hawthorne effect than measurement over a longer study period. It also suggests that studies with a lower risk of bias (for example, better blinding practices) see a lower control group adherence rate that is closer to that of the general asthma population. These studies may consequently see a greater effect size from interventions.

On the basis of the larger sample size and overall longer observation period, the combined cohort/control adherence estimate of 64.3% is likely to be the more useful measure of general population adherence. However, this is with the proviso that, for the reasons indicated, it is still likely to be an overestimate of real-world adherence, perhaps just as much as retrospective prescription data. This also has implications for what studies consider to be 'baseline' adherence and raises the question of whether true baseline adherence can truly be measurable using an EMD without truly covert monitoring (i.e. no study enrolment or change in inhaler device). As the vast

majority of inhalers do not incorporate such capabilities, this is not currently possible.

2.5.4. Interventional studies

This meta-analysis finds a significant difference between control and intervention group end of study adherence in RCTs. Adherence interventions ranged from speech recognition programmes to improve participant attitudes to their ICS to self-management programmes. As also noted by Normansell et al., this suggests that EMDs are an effective measure for detecting differences between good and poor adherence, important for both deployment in interventions and in clinical practice (46). The meta-analysis included studies using a range of EMDs, suggesting that effectiveness at this level is not necessarily dependent on more advanced EMD capabilities. It also suggests that, across a range of study designs, poor adherence does appear to be amenable to intervention. This should lend fresh impetus to addressing poor adherence in the clinical setting and to finding effective means of translating these potential gains to actual clinically meaningful changes for patients with poor adherence with potential benefit. This theme is explored in more detail in *Chapter 3*.

2.5.5. Heterogeneity and limitations of the review

This review was designed to capture as much of the existing evidence as possible and determine what could be inferred from it to enable progress in the field. Thus its main strength is that it provides a comprehensive picture of the state of the art of EMDs. As a result of this, however, it has of necessity captured studies which have differed in purpose, design and conduct over a period of almost three decades.

Examples of disparity in population beyond basic demographics included racial distribution, with some studies recruiting an overwhelmingly Caucasian population, whereas one study was 98% Afro-Caribbean. In some studies, participants were more likely to have fixed airflow obstruction or have been hospitalised due to their asthma than others. Some of these factors are known to impact on both adherence (62) and adverse risk (21).

Other areas of variation included what studies classed as EMDs, how the outcome of adherence was measured, how control groups were managed, and the nature of interventions. These factors have contributed to an extremely high level of heterogeneity, perhaps most clearly demonstrated in the meta-analysis (I^2 generally >75%). Lower degrees of heterogeneity were primarily noted (including in subgroupings) where studies were interventional in nature and where studies were deemed

to have a lower risk of bias by more stringent criteria, suggesting that study design and conduct are key to obtaining representative and generalisable data. Thus, whilst such a high degree of heterogeneity is a limitation of this review, it also highlights disparities in how these studies, including interventional studies, are conducted and controlled.

This impacts the confidence with which results of the meta-analysis can be asserted. As discussed, control groups provided with new inhalers, reimbursement, additional educational and motivational interventions, as well as experimental study conditions are likely to inflate a supposedly baseline population adherence. More stringent definitions of adherence may offer lower adherence results, whilst less stringent definitions offer higher results, increasing the confidence intervals around the estimate. Biases in study conduct may reduce the confidence of any interventional effect size. Finally, behavioural interventions using (for example) motivational interviewing differ from testing dosing regimes.

The nature of the evidence in this field as it stands is such that heterogeneity is inevitable. Attempts to minimise it would have led to more stringent inclusion criteria, reducing the breadth of the resulting data. Such a limited scope was not the aim of this review. However, the limitations which have been discussed are

important and the results of this review must be considered in light of them.

2.6. Conclusion

This review finds considerable differences between devices, device characteristics, definitions of adherence and study designs. Such widespread differences suggest a need for minimum standards in electronic monitoring of adherence.

The review suggests that EMDs are an effective means of detecting the difference between good and poor adherence for interventional studies. This review further finds an electronically monitored adherence rate in the literature of 64.3%. Studies in this area are, however, noted to be vulnerable to selection bias and observer effect and so it is probable that this rate over-estimates adherence in the asthma population as a whole.

Chapter 3: Electronic monitoring devices for improving adherence and clinical outcomes in asthma: A systematic review

3.1. Introduction

Adherence to inhaled corticosteroids (ICS) in asthma is thought to be poor. *Chapter 2* exclusively used electronic monitoring to estimate a population adherence rate of 64% based on cohort studies and interventional study control groups. A subset of studies from a recent systematic review measuring average ICS adherence in adults with asthma suggested adherence levels between 22 and 63% (50). The upper limit fell to 50% in database studies where participants would not have been aware that their behaviour was being watched i.e. removing the Hawthorne Effect.

Several factors have worked to support the increased prominence of identifying and modifying non-adherence. Firstly, it has been demonstrated that poor adherence to ICS and overuse of short-acting beta agonist (SABA) are associated with poor asthma outcomes, including risk of exacerbation, hospitalisation and death (30-32, 92, 150, 151). Secondly, due

to the advent of monoclonal antibody therapies with their associated increased cost and potential (if rare) adverse event profile, regulatory authorities now insist upon the measurement of adherence (5, 34). Thirdly, the advent of new inhaler technology makes objective monitoring more feasible.

Beyond merely monitoring adherence, a new role for inhaler technology is emerging with stakeholders exploring its potential to effect behaviour change and facilitate care in asthma (152-154). In *Chapter 2*, this thesis reviewed studies using electronic monitoring to measure adherence, but identified a need for in-depth assessment of electronic monitoring device (EMD) effectiveness when used as a tool for intervention. This chapter addresses this need. Proposed mechanisms for EMD-mediated behaviour change include targeting causes of unintentional non-adherence (e.g. forgetfulness), and providing objective adherence data as a springboard for investigating and addressing underlying difficulties. It is also possible that the user's knowledge that they are being observed may, at least temporarily, bring about improved compliance (the 'Hawthorne Effect' (155)).

3.2. Objectives

1) Primary objective: to assess whether EMD-based behavioural interventions have been demonstrated to improve ICS adherence for individuals with asthma in controlled studies
2) Secondary objectives:
    a) To assess whether improved adherence resulting from EMD-based behavioural interventions translated into improvements in clinical outcomes
    b) To examine the characteristics of studies where improved clinical outcomes were achieved in order to inform research in this area.

3.3. Methods

Medline, Scopus and Web of Science were searched by a single investigator for asthma studies using electronic monitors. Searches were completed July 2017 and updated January 2019. Due to the contemporary nature of the technology, no time limits were incorporated into the search criteria (see *Figure 3-1*). Studies were included if they were controlled and improvement in adherence (i.e. measured comparison over time between the prescribed and actual dose of ICS) was either a primary or secondary objective. Studies for both adults and children were included.

Figure 3-1: Search terms

Medline 295

((electronic and monitor* and asthma) or (inhaler and technology and (integrated and monitor)) or (asthmapolis or (doser and asthma) or (smartinhaler and tracker) or smarttrack or (turbuhaler and pneumotachograph) or (diskus and adherence and logger) or (inca and asthma) or (nebulizer and chronolog) or mdilog or smartmist or smarttouch or (propeller and asthma) or (Asthma and (smartdisk or smartturbo or smartflow or smartmat or smartspray)))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
+1 (turb**o**haler and pneumotachograph).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
(dis**c**us and adherence and logger).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
Scopus 511

(TITLE-ABS-KEY ((electronic AND monitor*) AND asthma)) OR ((TITLE-ABS-KEY (inhaler AND technology)) AND (integrated AND monitor)) OR (TITLE-ABS-KEY (asthmapolis OR (doser AND asthma) OR (smartinhaler AND tracker) OR (smarttrack) OR (turbuhaler AND pneumotachograph) OR (diskus AND adherence AND logger) OR (inca AND asthma) OR (nebulizer AND chronolog) OR (mdilog) OR smartmist OR smarttouch OR (propeller AND asthma))) OR (ALL (asthma AND (smartdisk OR smartturbo OR smartflow OR smartmat OR smartspray)))
+1 turb**o**haler and pneumotachograph
dis**c**us and adherence and logger
Web of Science 359

TS=((electronic monitor* AND asthma) OR (inhaler technology AND (integrated monitor)) OR (asthmapolis OR (Doser AND Asthma) OR (Smartinhaler Tracker) OR SmartTrack OR (Turbuhaler AND pneumotachograph) OR (Diskus adherence logger) OR (INCA AND Asthma) OR (Nebulizer Chronolog) OR MDILog OR SmartMist OR SmartTouch OR (Propeller AND Asthma) OR SmartDisk OR SmartTurbo OR SmartFlow OR SmartMat OR SmartSpray)) OR TI=((electronic monitor* AND asthma) OR (inhaler technology AND (integrated monitor)) OR (asthmapolis OR (Doser AND Asthma) OR (Smartinhaler Tracker) OR SmartTrack OR (Turbuhaler AND pneumotachograph) OR (Diskus adherence logger) OR (INCA AND Asthma) OR (Nebulizer Chronolog) OR MDILog OR SmartMist OR SmartTouch OR (Propeller AND Asthma) OR SmartDisk OR SmartTurbo OR SmartFlow OR SmartMat OR SmartSpray))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=1900-2017
+1 turb**o**haler and pneumotachograph
dis**c**us and adherence and logger

Titles abstracts and full texts were assessed for eligibility. Data were extracted from the published full texts and supplements/study protocols where readily available for narrative synthesis. Data extracted included study design and *a priori* objectives, the nature and role of EMDs used, sample

size calculations and baseline population characteristics, with a particular focus on characteristics suggestive of a target population likely to benefit from EMD-based interventions. Outcome measures including measures of adherence, symptom control questionnaires, spirometry, and markers of exacerbation were also extracted. Author comments on EMD reliability and study limitations were noted.

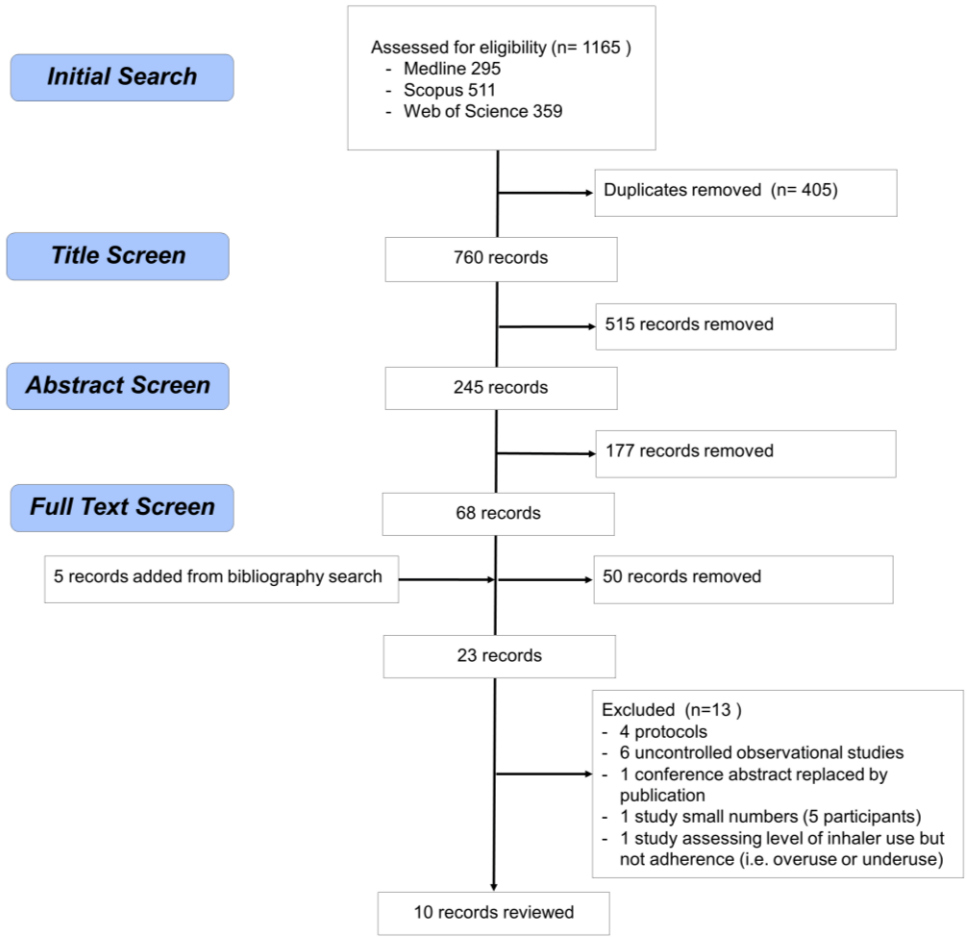
A meta-analytic synthesis was not conducted. As noted in *Chapter 2*, there was a significant degree of heterogeneity even between interventional studies. Even though this review was designed to have a narrower remit, it was still designed to capture a range of interventions, which would render a meta-analysis susceptible to any of the same concerns as discussed regarding the interventional studies in *Chapter 2*.

3.4. Results

A flow diagram of included studies from the July 2017 search is shown below *(Figure 3-2)*. Ten studies published between 2003 and 2018 were identified from 1963 records screened: 1165 screened from the initial search and 798 screened from bibliography searches (67-71, 99, 100, 118, 156, 157). From the January 2019 update, 271 new titles were identified, 33 of

which met the criteria for abstract screen and one of which met criteria for inclusion in this review (158).

Figure 3-2: EMD as intervention - study flow



Included studies had a combined population of 1510 participants from Australia, the Netherlands, New Zealand, the Republic of Ireland, the United Kingdom and the United States of America. The studies lasted between ten weeks and twelve

months with a median duration of six months. Mean age ranged from 5.9 to 53.0 years.

3.4.1. Study design

Five of the studies reviewed were in adults only (68, 99, 100, 118, 157), one (classified in this review as an adult study) recruited adults and adolescents (67) and the remaining five studies were in children (69-71, 156) (*Table 3-1*). Nine studies were reported as randomised controlled (67, 69-71, 99, 100, 118, 156, 158), one as cluster-randomised, controlled (68) and one as cluster controlled (157) (*Table 1*).

As with *Chapter 2*, significant heterogeneity is noted in the studies included in this review. Even accounting for population age (the review includes studies across the lifespan), there was significant heterogeneity in baseline reported ICS dose and in baseline adverse risk profile (i.e. lung function and exacerbation history). *Table 3-1* further highlights differences in the kinds of interventions.

The studies tested the following interventions:

- EMD + reminder (67, 70, 71, 158)
- EMD + feedback/behavioural intervention (100, 118, 156)

- EMD + reminder + feedback/behavioural intervention (68, 69, 99, 157)

Reminders were essentially integrated alarm systems which would sound in the event of missed doses. Feedback involved adherence discussions based on EMD-derived adherence data. Two studies tested more standardised, evidence-based behavioural research as part of the intervention. One tested a *"problem solving approach"*, individualised conversations successfully trialled in diabetes which involved addressing barriers with agreed solutions that were then evaluated and adapted (118). The second tested *"personalised adherence discussions"*, a form of motivational interviewing conducted by the patient's own primary care practitioner who had been trained in the technique (68).

There were also differences in EMDs and their capabilities. Adherium's Smartinhaler™ was the most commonly used EMD brand, used in six of the studies (67-69, 71, 156, 157). These EMDs did not account for inhaler technique in adherence calculations as the INCA device does. Finally, again similar to the previous review, *Table 3-1* demonstrates considerable variation in what is constitutes a 'control' group.

Table 3-1: Review of EMD-based interventional studies – study information

First Author	Year	Country	Study Type	Adults/ Children	Follow-up	Interventions	Control	EMD
Apter (118)	2011	The United States of America	Randomised controlled	Adults	6 months (26 weeks) 2 week run-in (baseline - week 2) Intervention initiation (week 2) 3 months intervention (months 1, 2, 3) 3 months observation (months 4, 5, 6)	Problem solving (PS) intervention = 4x30 min sessions *"Non-judgemental"* feedback of ICS electronic monitoring device (EMD) data to inform PS feedback (improve or maintain adherence)	EMD, standard *"didactic"* asthma education	Diskus Adherence Logger (DAL, developed by research group) MDI-Log (commercially available)
Burgess (156)	2010	Australia	Randomised controlled	Children	4 months Baseline Months 1, 2, 3, 4	Feedback of preventer EMD data to parent, child and physician, incorporated into management plan for following month	EMD, no feedback	Smartinhaler™ (commercially available, reference to validation study)
Chan (71)	2015	New Zealand	Randomised controlled	Children	6 months Baseline Months 2, 4, 6	EMD, audio-visual reminder (AVR) enabled	EMD, no AVR	SmartTrack Smartinhaler™ (commercially available, reference to reliability study)
Charles (67)	2007	New Zealand	Randomised controlled	Adolescents and adults	6 months Baseline (-2 weeks), Weeks 0, 6, 12, 18, 24	EMD, AVR enabled	EMD, no AVR	Smartinhaler™ (commercially available)
Foster (68)	2014	Australia	Pragmatic cluster-randomised controlled (2x2 factorial parallel group)	Adults	6 months General Practitioners (GP): Baseline Week 4 Investigators: Week 1 Months 2, 4, 6	Inhaler reminders and feedback (IRF) group: EMD, AVR option enabled/online automated reports + GP feedback at four weeks/inter-current review IRF + Personalised adherence discussions (PAD) group: EMD, AVR option enabled/online automated reports + GP feedback with personalised GP-led PAD discussions	EMD, usual care or EMD, PAD	SmartTrack, Smartinhaler™ (commercially available, reference to reliability study)

First Author	Year	Country	Study Type	Adults/ Children	Follow-up	Interventions	Control	EMD
Kenyon (158)	2018	The United States of America	Randomised controlled	Children	1 month Baseline 30 days	EMD, Way to Health platform text messaging	EMD, no text	Propeller
Kuipers (157)	2017	The Netherlands	Cluster controlled	Adults	6 months Baseline, Intervention group - 2 weekly CARAT* scores, feedback if low/deterioration or not completed, All - Month 6	Initial visit with 1:1 counselling Two-weekly CARAT questionnaire with automated feedback/personalised feedback for low or deteriorating scores EMD + app reminder/visual app adherence feedback EMD + app/visual app adherence feedback + feedback to pharmacist + CARAT questionnaire/feedback	No CARAT questionnaire/ feedback, no EMD/app, usual care	SmartTurbo Smartinhaler™ (commercially available, reference to validation data) using TurbuPlus platform (AstraZeneca)
Morton (69)	2017	The United Kingdom	Randomised controlled	Children	12 months Baseline Months 3, 6, 9, 12	EMD, AVR enabled + adherence feedback informing personalised management strategies	EMD, no AVR or feedback - standard asthma review	SmartTrack and SmartTurbo Smartinhaler™ (commercially available, reference to validation data)
Onyirimba (100)	2003	The United States of America	Randomised controlled	Adults	10 weeks Baseline Days 7, 14, 21, 42, 70	Direct feedback on ICS use by a "clinician investigator"	EMD, usual care	MDI Chronolog (commercially available)
Sulaiman (99)	2018	The Republic of Ireland	Randomised controlled	Adults	3 months Baseline Months 1, 2, 3	EMD, direct (bio)feedback on inhaler use (technique and temporal adherence)	EMD, no (bio)feedback, intensive education	INCA (developed by research group, reference to validation studies)
Vasbinder (70)	2016	The Netherlands	Randomised controlled	Children	12 months Baseline Months 3, 6, 9, 12	EMD + tailored short messaging service (SMS) reminders	EMD, no tailored SMS reminder	E-haler Adhaler (commercially available)

** Control of Allergic Rhinitis and Asthma Test (CARAT)*

Six studies reported allocation concealment (67-71, 156) (see also *Table 3-2*). Methods of blinding reported included blinding participants to the study hypothesis (100) and fully covert monitoring either for all participants (67, 71) or for control participants/clinicians (68). They also included blinding the research team collecting participant data, delivering standard care or delivering interventions (68, 100). Three studies did not specify such blinding, but did specify that control participants' adherence data was not looked at by study team in contact with the participant for the duration of the study (69, 156, 159). In one study, neither participants nor the research team had access to the data until the end of the intervention period, although it did not specify whether the team had access to data prior to other outcome measurement (158). One study only downloaded participant data once study visit procedures were complete (67). Only one study specified researcher blinding for any part of the analysis (159) (*Table 3-2*).

Table 3-2: Review of EMD-based interventional studies – study design

First Author	Study hypothesis	Participant blinding	Investigator blinding	Compensation
Apter (118)	Use of a PS *vs.* standard asthma education (AE) *"improves adherence and asthma-related health outcomes*".	Blinded to hypothesis but not to (EMD) function	Not reported	Financial incentives ICS supplied if no insurance coverage or reimbursed if co-payment
Burgess (156)	*"Measuring [preventer] adherence in children with unstable asthma and providing feedback [increases] adherence over the medium term."*	Deliberate blinding not reported	Study team delivering control management blinded to control adherence	Not reported
Chan (71)	EMD with AVR improves adherence and asthma outcomes in school-age children following emergency department (ED) attendance for asthma exacerbation.	Blinded to EMD function/study hypothesis (covert monitoring)	Not reported	Participants provided with inhalers
Charles (67)	An EMD with AVR improves ICS adherence in adult asthma.	Blinded to EMD function/study hypothesis (covert monitoring)	No intentional blinding reported, however data at each visit only downloaded after study participant had completed study procedures.	Not reported
Foster (68)	Use of IRF, PAD incorporating Information-Motivation-Behavioural skills model, or a combination of the two (IRF + PAD) improves adherence to combination ICS/long-acting beta agonist (LABA) inhaler and asthma control in poorly controlled, moderate-severe asthma compared with usual care (UC).	Partially blinded- PAD/UC participants not informed of EMD function (covert monitoring). All participants blinded to study hypothesis.	GPs randomised to a single intervention and blinded to other interventions. Minimal investigator involvement – study visits at baseline and 4 weeks conducted by GP. Investigator collecting telephone data blinded to study group. All other questionnaires via post. MiniWright Digital spirometer supplied to participants.	One salbutamol inhaler and one month's fluticasone/salmeterol, peak flow/forced expiratory volume in one second (FEV_1) monitor supplied.
Kenyon (158)	A daily reminder text message intervention in a cohort of high risk children improves electronically monitored adherence following emergency department attendance or hospital admission for exacerbation of asthma.	Participants in both arms provided with a "control" version of the app for data transmission purposes only. Blinding to purpose of EMD function not reported.	Not reported. Study team unable to access data during intervention but unclear whether accessed prior to outcome data collection.	$60 ($20 per survey at baseline, 30 days and 60 days)

First Author	Study hypothesis	Participant blinding	Investigator blinding	Compensation
Kuipers (157)	*"Prospective monitoring with patient-reported CARAT scores"* informing *"tailored pharmacists' interventions"* improves asthma control compared with usual care.	Partially blinded to hypothesis	Unblinded – all pharmacists have EMD data available but only intervention pharmacists to use, however control pharmacists did not have scheduled follow-up contact with participants.	Not reported
Morton (69)	Use of EMD with AVR and feedback in the routine clinical setting with children with poorly controlled asthma would, *"by addressing both the intentional and non-intentional adherence barriers",* increasing adherence rates *"to a degree necessary to improve asthma control and clinical outcomes."*	Not blinded	Control group clinicians blinded to adherence data.	Not reported
Onyirimba (100)	Use of *"direct, non-judgemental clinician-to-patient feedback of inhaled steroid use"* improves adherence compared with usual care.	Blinded to study hypothesis, no blinding to EMD function	Study staff delivering standard care blinded to study group for intervention visits. Clinicians blinded to control adherence data.	ICS and salbutamol supplied to self-pay participants
Sulaiman (99)	*"Visual (bio)feedback to the patient of their specific components of adherence [improves] adherence."*	Not blinded to study hypothesis or EMD function but control group are blinded to own adherence data	Automated adherence analysis; validated by two raters unaware of study group or clinical outcomes and uninvolved in clinical care.	Salmeterol/fluticasone discus supplied by study team with INCA device loaded, exchanged monthly
Vasbinder (70)	EMD with tailored SMS reminders *"[improves] adherence to ICS and… subsequently… asthma control, asthma-related quality of life and [reduces] asthma exacerbations"* compared to EMD alone.	Not blinded	Not reported	Not reported

Nine studies reported power calculations, five for adherence only (67, 70, 99, 118, 156), two for outcomes in asthma only (68, 69) and two for both (71, 157) (*Table 3-3*). Of note is the degree of variation in the ideal sample sizes required by these different power calculations. Four did not meet their recruitment targets (68, 70, 99, 118). Three studies reporting recruitment by group, study retention and primary analysis (i.e. intention to treat *vs.* per protocol) were fully powered for their intention to treat analysis (69, 71, 99).

3.4.2. Population characteristics

Most studies had majority female participants (67, 68, 70, 99, 100, 118, 156, 157) as shown in *Table 3-4*. Three studies measured baseline adherence – one objectively (157), one subjectively (158) and one both objectively and subjectively (118), also shown in *Table 3-4*. Subjective asthma control was generally measured by validated questionnaire. Three of the four studies in children reporting use of the Childhood Asthma Control Test (C-ACT™) or Asthma Control Questionnaire (ACQ) showed baseline uncontrolled asthma (69, 71, 158). In adults, all four studies reporting control by questionnaire showed mean values consistent with uncontrolled asthma (68, 99, 118, 157).

Table 3-3: Review of EMD-based interventional studies – study power

First Author	Sample Size Power Calculation	Effect size - Adherence	Effect size - Other	Randomised/ Allocated	Completed – Overall (% allocated)	Completed - Intervention (IG)	Completed - Control (CG)	Analysis model	Analysed	Analysed (% allocated)	Analysed (% powered)
Apter (118)	330 overall	10%	-	333		Not reported	Not reported	Intention to treat (ITT)	Not reported		
Burgess (156)	20 overall	20%	-	26	26 (100)	14	12	Not reported	14 IG* / 12 CG†	100	130
Chan (71)	Per group: 51 (adherence) 84 (schooldays) 100 (morbidity)	10%	Schooldays missed 6 day drop, asthma morbidity score 30% reduction	220	213 (97)	108	105	ITT	110 IG / 110 CG	100	216
Charles (67)	100	10%	-	110	90 (82)	44	46	Apparent per protocol	44 IG / 46 CG	82	90
Foster (68)	Over-recruit to 220 (to allow for 15% attrition)	-	Improvement in ACT™‡ ≥1.5 points	60 GPs 143 patients	43 GPs 129 patients (90)	PAD – 21 patients IRF – 35 patients IRF + PAD – 32 patients	41 patients	ITT (primary analysis)	21 PAD / 35 IRF / 32 IRF + PAD / 41 UC	90	69
Kenyon (158)	-	-	-	41	32 (78)	15	17	Apparent per protocol	15 IG / 17 CG	78	
Kuipers (157)	Over-recruit to 80 (to allow for 5% attrition)	15%	CARAT: 4 point difference	80	68 (85)	CARAT + TurbuPlus - 16 CARAT only - 19 TurbuPlus only - 16	17	Not reported	39 EMD / 41 No EMD	100	105
Morton (69)	76 overall (over-recruit to 90 to allow for 15% attrition)	-	ACQ: 0.5	90	77 (86)	39	38	ITT	47 IG / 42 CG	99	117
Onyirimba (100)	-	-	-	30	19 (63)	10	9	Apparent per protocol	10 IG / 9 CG	63	
Sulaiman (99)	200	10%	-	218 111 - IG 107 - CG	195 (89)	100	95	ITT	105 IG / 101 CG	94	103
Vasbinder (70)	110 per group	15%	-	219 108 - IG 111 - CG	209	101	108	ITT	101 IG / 108 CG	95	95

** Intervention group (IG)*
† Control group (CG)
‡ Asthma Control Test™ (ACT™)

Table 3-4: Review of EMD-based interventional studies – baseline characteristics

First Author	Mean Age	Sex	Asthma Control	Asthma Quality of Life	Mean FEV_1 (%Predicted)	≥1 Exacerbation in previous 12 Months	ICS dose (Range)	Baseline Adherence	Between- Group Differences at Baseline
Apter (118)	Overall: 49 (14) IG: 49 (13) CG: 49 (14)	Female Overall: 241 (72%) IG: 122 (74%) CG: 119 (71%)	Mean ACQ Overall: 1.67 IG: 1.68 / CG: 1.65	Mini-AQLQ* Overall: 4.0 IG: 4.0 CG: 4.0	Overall: (66%) IG: (66%) CG: (64%)	ED Overall: 172 (52%) IG: 86 (52%) CG: 86 (51%) Hospitalisation Overall: 103 (31%) IG: 52 (32%) CG: 51 (30%)	Not reported	Subjective (questionnaire) and objective (electronically monitored)	P values not significant
Burgess (156)	IG: 9.1 CG: 9.3	Male IG: 11 *(42.3%)* CG: 7 *(26.9%)*	Symptoms or reliever use ≥3x in last week IG: 10 (38.5%) CG: 8 (30.8%)	Not measured	IG: (72.9%) CG: (77.5%)	Not measured	Mean daily dose IG: 300 mcg (200-500) CG: 250 mcg (50-500)	Not measured	P values not significant
Chan (71)	IG: 8.9 CG: 8.9	Male IG: 55 (50%) CG: 58 (53%)	Mean C-ACT™ IG: 18.8 / CG: 18.8 Mean asthma morbidity score IG: 9.3 / CG: 9.2	Not measured	IG: (92%) CG: (90%)	ED Overall: 100% (inclusion criterion)	Not reported	Not measured	None reported
Charles (67)	Median IG: 39 (13-65) CG: 35 (15-64)	Male IG: 28 *(50.9%)* CG: 22 *(40%)*	Not measured	Not measured	PEF† IG: 434 / CG: 444	Not measured	Median daily dose IG: 500 mcg (100-2000) CG: 500 mcg (100-4000)	Not measured	Reported as nil

First Author	Mean Age	Sex	Asthma Control	Asthma Quality of Life	Mean FEV_1 (%Predicted)	≥1 Exacerbation in previous 12 Months	ICS dose (Range)	Baseline Adherence	Between- Group Differences at Baseline
Foster (68)	Overall: 40.3 (15.2) PAD: 42.3 (15.6) IRF: 40.0 (13.7) IRF + PAD: 39.7 (17.7) UC: 40.0 (14.1)	Female Overall: 62% PAD: 54% IRF: 49% IRF + PAD: 78% UC: 63%	ACT™ Overall: 14.6 PAD: 14.7 IRF: 15.1 IRF + PAD: 14.1 UC: 14.6	Not measured	Overall: 77.1 (20.3) PAD: (67.3%) IRF: (84.4%) IRF + PAD: (78.0%) UC: (75.7%)	Overall 32% PAD 50% IRF 23% IRF+PAD 34% CG 29%	Mean daily dose Overall: 718 mcg PAD: 722 mcg IRF: 704 mcg IRF + PAD: 777 mcg UC: 683 mcg	Not measured	Lower proportion of men in IRF+PAD Differences in proportion of current smokers
Kenyon (158)	Overall: 5.9 (2.1) IG: 6.1 (2.1) CG: 5.8 (2.1)	Male Overall: 22 (54%) IG: 12 (57%) CG: 10 (50%)	Mean C-ACT™ Overall: 17.3 (4.4) IG: 17.8 (4.3) CG: 17.2 (4.6)	Not measured	Not measured	Mean ED visits Overall: 1.0 (1.5) IG: 1.0 (1.5) CG: 1.0 (1.6) Mean hospitalisations Overall: 0.4 (0.7) IG: 0.3 (0.6) CG: 0.5 (0.8)	Not reported	Mean Care-giver reported Overall: 64% (24%) IG: 65% (23%) CG: 62% (25%)	Caregiver education level higher in control group
Kuipers (157)	**EMI‡ vs. No** IG: 44.08 (6.93) CG: 40.17 (12.71)	**EMI vs. No** Female IG: 21 (53.8%) CG: 29 (70.1%)	**EMI vs. No** CARAT lower airways IG: 12.95 / CG: 12.98 CARAT total IG: 20.95 / CG: 20.73	Not measured	Not measured	**EMI vs. No** Mean (range) No of OCS§ courses **6 months** IG: 0.10 (0-2) CG: 0.12 (0-1)	Not reported	**EMI vs. No** Dispensing data (%PDC¶) IG: 82.38 CG: 75.42	Mean age higher in IG (CARAT) group
Morton (69)	IG: 10.4 (2.9) CG: 10.2 (2.9)	Male IG: 28 (60%) CG: 22 (52%)	ACQ IG: 2.5 / CG: 2.3	Mini-PAQLQ# IG: 4.3 CG: 4.6	IG: (87.2%) CG: (88.0%)	**Previous 3 months:** Number of OCS courses IG: 1.2 / CG: 1.2 ED/GP visit IG: 1.9 / CG: 2.1 Hospitalisation IG: 0.3 / CG: 0.2	Mean dose IG: 697.9 mcg CG: 664.3 mcg	Not measured	Not reported
Onyirimba (100)	IG: 45 (11) CG: 53 (14)	Female Randomised: 26 (86.7%) Analysed: 16 (84.2%)	Not measured	AQLQ IG: 4.34 CG: 3.75	IG: (78%) CG: (63%)	ED IG: 2.3 / CG: 1.0	IG: 946 mcg CG: 928 mcg	Not measured	Reported nil for demographics, FEV_1 % predicted, AQLQ, ICS dose

First Author	Mean Age	Sex	Asthma Control	Asthma Quality of Life	Mean FEV_1 (%Predicted)	≥1 Exacerbation in previous 12 Months	ICS dose (Range)	Baseline Adherence	Between- Group Differences at Baseline
Sulaiman (99)	Overall: 49.2 IG: 48.2 CG: 50.3	Female Overall: 64% IG: 67% CG: 63%	ACT™ Overall: 12.1 IG: 12.5 / CG: 11.7	AQLQ Overall: 3.7 IG: 3.7 CG: 3.6	Overall: 2.2 L (73.0%) IG: 2.2 L (75.1%) CG 2.1 L (70.8%)	Number of OCS courses Overall: 3.9 IG: 4.1 / CG: 3.8	Proportion on 500mcg ICS device Overall: 65% IG: 64% / CG: 65%	Not measured	P values not significant
Vasbinder (70)	IG: 7.8 (2.2) CG: 7.7 (2.1)	Male IG: 59 (58.4%) CG: 72 (66.7%)	C-ACT™ IG: 20.6 CG: 20.4 Proportion C-ACT™ ≤19 IG: 39 (39.8%) CG: 38 (36.5%)	PAQLQ IG: 6.1 CG: 5.9	Not measured	Not measured	Not reported directly as daily dose	Not measured	None reported

** Asthma Quality of Life Questionnaire (AQLQ)*
† Peak expiratory flow (PEF)
‡ Electronic monitoring of the intake of inhalation medication (EMI)
§ Oral corticosteroid (OCS)
¶ Proportion of days covered (PDC)
 # Paediatric Quality of Life Questionnaire (PAQLQ)

Eight studies reported baseline exacerbations. Two of the three paediatric studies reporting baseline exacerbations had populations which, on average, suffered at least one exacerbation within the three months preceding enrolment (69, 71). Four adult studies reported exacerbations within the preceding year (99, 100, 118, 157), with the reported proportion of participants who had exacerbated ranging between 32% and 100% (*Table 3-4*). One adult study reported exacerbations in the preceding six months but had a mean rate of 0.10 oral corticosteroid (OCS) courses per intervention participant and 0.12 courses per control participant (157).

3.4.3. Outcomes

Adherence

Adherence was generally measured as an average percentage of the doses taken over a specified period of time divided by the number of doses prescribed and capped at a maximum of 100% i.e. overuse of ICS was not included in the adherence measure (*Table 3-5*). Kuipers et al. used a prescription measure as their outcome adherence measure (157). Three studies specifically reported on ICS overuse (67, 99, 100). One study also assessed the quality of the dose taken (99).

Eight studies reported absolute differences in average adherence between control and intervention arms, ranging

between 10% and 54% (*Table 3-6*). The largest differences were recorded by Chan et al. in children (71), and Onyirimba et al. in adults (100), described in *Table 3-6*. One study did not report an absolute difference but noted a four-fold higher adherence in their EMD group versus their non-EMD group (157). Only two of the eleven studies observed no improvement in adherence after use of an EMD as part of an adherence intervention (118, 158). However, one of these studies did find that participants with low social support, higher exposure to violence and low income did have a higher adherence in response to the intervention (118).

Of studies reporting adherence over time, three showed decline (including a decay of any gains made in adherence) across both intervention and non-intervention arms (68, 71, 118). Two showed initial decline (over the first halves of a six and twelve month study respectively) and then stabilisation (67, 70). The remainder showed a separation between the intervention group and control groups, the former of which were able to maintain their gains in adherence (69, 99, 100, 156).

Table 3-5: Review of EMD-based interventional studies – outcome measures and results

First Author	Primary Outcome Measure	Secondary Outcome Measures	Significant Primary Outcomes	Significant Secondary Outcomes
Apter(118)	Adherence to ICS regimen prescribed by the patient's physician = (number of actuations downloaded/number prescribed) x 100) truncated at 100%	1. Mini-AQLQ 2. ACQ 3. Spirometry 4. ED/hospital for asthma 5. ED/hospital for any cause	Reduction in adherence by 10% in intervention group and 14% in control group (p=0.0004). Post-hoc better adherence with intervention if baseline low social support (p=0.003), high exposure to violence (p=0.007) and low income (p=0.03).	Improved ACQ (p=0.002), mini-AQLQ (p<0.0001), first and second visit FEV_1 (p<0.01) in both groups (no significant difference between groups). Post-hoc significant AQLQ improvement if baseline low CES-D* scores (p=0.007). Post-hoc significant FEV_1 improvement if baseline low AQLQ (p=0.03) or numeracy (p=0.007).
Burgess (156)	Adherence to ICS =% of prescribed doses (midday/midnight for twice daily dosing)	1. History of symptoms > twice in a week requiring reliever 2. FEV_1 % predicted *NB Not specified in methodology*	Mean adherence 79% in active *vs.* 57.9% in control (p<0.01). Control group adherence deteriorated slightly over study course, intervention group adherence rose (p<0.01).	Symptom control as measured by reported reliever use significantly improved in both groups (p=0.02). FEV_1 improved significantly in both groups - baseline 75% to 85.2% (p<0.01).
Chan (71)	Adherence to ICS = degree of deviation from prescribed dose subtracted from 1 (max 0% non- adherence) - measured midday/midnight School day absence (proportion of total number of possible schooldays missed)	1. Asthma morbidity score 2. C-ACT™ 3. FEV_1 % predicted 4. ED attendance 5. Caregiver work absence 6. >=1 day 7. Exacerbations 8. Number of days of reliever use (electronically monitored)	Median percentage adherence 84% in intervention *vs.* 30% in control (p<0.0001). Higher proportion in intervention group had adherence >70%. Fall in overall adherence in both groups at same rate.	Greater improvement in asthma morbidity score in intervention group (2.0 *vs.* 1.2 point reduction, p=0.008). C-ACT™ significantly different at 2, 4 and 6 months (p<0.0001) although no significant improvement with time beyond 2 months. Improvement in reliever use (median 9.5% days intervention *vs.* 17.4% control, p=0.002). Difference in exacerbations at 0-2 months (7 *vs.* 26, p=0.015) but nil thereafter. Significant improvement in FEV_1 in both groups (p=0.0003).

First Author	Primary Outcome Measure	Secondary Outcome Measures	Significant Primary Outcomes	Significant Secondary Outcomes
Charles (67)	Adherence to ICS (2 doses 6 hours apart calculated as a proportion of prescribed doses % truncated at 100% - doses after midnight counted for previous day if before going to bed)	1. >50%/80%/90% adherence 2. Proportion of medication taken as prescribed in 2 week periods around appointments 3. Proportion of medication taken as prescribed in 4 week periods between clinic assessments 4. >50%, >80%, >90% 5. PEF 6. ACQ 7. Rates of dose dumping	In final 12 weeks, median adherence was 93% intervention *vs.* 74% in control (p<0.0001). Mean values for the same period were 88% intervention *vs.* 66% in control.	Taking >50% medication 95.5% intervention *vs.* 71.7% control (p=0.003). Taking >80% medication 88.6% intervention *vs.* 39.1% control (p<0.0001). Taking >90% medication 63.6% intervention *vs.* 19.6% control (p<0.0001). Fall in overall adherence in both groups in first 12 weeks, stable for next 12 weeks. Final 4 weeks, intervention group underestimated missed doses by mean of 3, control by mean 12.2 (p=0.001). Dose dumping 10 occasions in intervention and 43 occasions in control group (p=0.008).
Foster (68)	ACT™	1. Mini-AQLQ 2. HADS[†] 3. MARS-A[‡] 4. FEV_1 5. Prednisolone courses (severe exacerbations)	ACT™ improvement all groups (overall mean change 4.5, p<0.0001, clinically meaningful threshold surpassed).	Significantly higher adherence in both IRF *vs.* non IRF (73% *vs.* 46%, p<0.0001). Adherence decreased in all groups over time. Overall improvements in AQLQ (p<0.0001), anxiety (p=0.022), MARS-A (p=0.008).
Kenyon (158)	Feasibility	1. 30 day ICS adherence 2. 30 day change in C-ACT™		
Kuipers (157)	CARAT	1. MARS-5[§]/ICS refill (PDC) adherence 2. Exacerbations (pharmacy systemic steroid dispensing data)		4.52 fold increase in refill adherence >80% in subgroup provided with EMD compared to no EMD (95% CI 1.56- 13.1).

First Author	Primary Outcome Measure	Secondary Outcome Measures	Significant Primary Outcomes	Significant Secondary Outcomes
Morton (69)	ACQ	1. FEV_1 % predicted 2. GP/ED asthma unplanned attendance 3. Number of OCS courses reported 4. Number of days of school due to asthma reported 5. Reported beta agonist use 6. BTS[#] level of asthma therapy 7. Mini PAQLQ 8. Adherence per 3 months (mean daily actual/prescribed x100) capped at 100% 9. Parental BMQ** 10. Parental IPQ[††]	ACQ decreased in both groups exceeding MID[¶] by month 3 and maintained until month 12.	Adherence 70% over 12m for intervention group *vs.* 49% for controls (p≤0.001). Adherence maintained for 12 month period for adherence group but fell in controls. 20 intervention participants *vs.* 6 controls had >80% adherence maintained for the 12 months. 4 intervention participants *vs.* 11 controls had rates <30%. FEV1 improved in both arms with no sig diff between arms at 12m Intervention has lower event rate for OCS courses (p=0.008) and hospital admissions (p<0.001).
Onyirimba (100)	ICS adherence = mean weekly adherence (actuations/prescribed x 100 for each day truncated to 100%) and percentage days overuse	1. Daily albuterol electronically monitored (mean actuations/24h per week) 2. Nighttime albuterol electronically monitored (mean nightly (1-5am) actuations per week) 3. AQLQ 4. FEV_1	Adherence comparable at wk 1 (61% *vs.* 51%) but separation at wk 2 (81% intervention *vs.* 47% control, p=0.003) maintained to the end of the study (p<0.0001). Control adherence declined to below 30% at wk 10, however from week 2 onwards, intervention group adherence maintained at >70%.	AQLQ improved from baseline in both groups (p<0.05).
Sulaiman(99)	Rate of actual adherence at 3 months (cumulative drug exposure in final month)	Combined measure of asthma control generated from PEF, ACT™, AQLQ and adherence.	Mean actual adherence 73% in intervention *vs.* 63% in controls (p≤0.01). Greater change in adherence over study period in intervention *vs.* control (p=0.02). Increase in intervention adherence over study period by 7.5% (p<0.01), fall in control group by 3.4% (p<0.01).	52 (35%) uncontrolled overall with adherence <80%. 40 (27%) uncontrolled with adherence >80%. 0 cases of attempted dose dumping in intervention *vs.* 14 cases in control.

First Author	Primary Outcome Measure	Secondary Outcome Measures	Significant Primary Outcomes	Significant Secondary Outcomes
Vasbinder (70)	Temporal ICS adherence = proportion of prescribed doses recorded as taken within 6 hours (3 hours pre-, 3 hours post-) of planned dose.	1. C-ACT™ 2. Severe exacerbation frequency (ED/hospitalisation/systemic corticosteroids) 3. PAQLQ 4. Costs (health and societal)	Adherence was 69.3% in intervention *vs.* 57.3% in control (95% CI for difference 6.7-17.7%). Estimated treatment effect significant for both first and second 6 month periods but larger in first 6 months, adherence declined in both groups in first 6 months then remained static.	

** Center for Epidemiologic Studies Depression (CES-D) Scale*
† Hospital Anxiety and Depression Scale (HADS)
‡ Medication Adherence Report Scale for Asthma (MARS-A)
§ Medication Adherence Report Scale (MARS)
¶ Minimally important difference (MID)
 # British Thoracic Society (BTS)
*** Beliefs about Medicines Questionnaire (BMQ)*
†† Brief Illness Perceptions Questionnaire (IPQ)

Table 3-6: Review of EMD-based interventional studies – summary of key adherence and clinical outcome findings and EMD performance

First Author	Difference in Adherence between Intervention and Control Groups	Significant Asthma Outcomes	EMD Pre-test and Study Performance
Apter(118)	3% difference in means, not significant.	Nil	Monitor download failure Overall: 380 (20%) / Intervention: 18% / Control: 22%
Burgess (156)	21% difference in means (p<0.01)	Nil	Not reported
Chan (71)	54% difference in medians (p<0.0001) 52% difference in means	Greater improvements in asthma morbidity score and ACT™ in intervention group over study period. Lower median reliever use in intervention group over study period. Lower patient-reported exacerbation rates in intervention group at two months; however this difference did not persist.	Devices not returned Overall preventer: 16 (2%) Overall reliever: 65 (9%) Complete download available Overall preventer: 678 (all remaining) Overall reliever: 632 (all remaining)
Charles (67)	19% difference in medians (p<0.0001) 22% difference in means	Nil	Not reported
Foster (68)	27% difference in means (p <0.0001)	Nil	5 devices failed in study, no data available for 6/143 due to device failures, 15 couldn't be contacted to activate device, 8 lost device.
Kenyon (158)	4% difference in adjusted means, not significant	Nil	6 couldn't be contacted to activate device; 3 had devices which only began to work after 30 day intervention period
Kuipers (157)	ICS refill >80% 4.52-fold (95% CI 1.56-13.1)	Nil	Not reported
Morton (69)	21% difference in means (p≤0.001)	Fewer courses of OCS (p=0.008) and hospital admissions (p<0.001) in intervention group.	Reported broken: Intervention: 23 (50%) / Control: 8 (19%) Objectively damaged: Intervention: 17 (37%) / Control: 2 (5%) Forgotten: Intervention: 10 (22%) / Control: 18 (43%) Lost: Intervention: 5 (11%) / Control: 2 (5%)
Onyirimba (100)	34% difference in means week 2 (p=0.003) >40% study end (visual examination of graph)	Nil	Not reported
Sulaiman(99)	10% difference in rates (p≤0.01)	Nil	Intervention group 12 device failures Control group 35 device failures (603 devices returned - see consort diagram - giving a failure rate of 7.79%)
Vasbinder (70)	12% mean (95% CI 6.7-17.7%)	Nil	Not reported

Asthma control

At two months, Chan et al. reported a significant difference between study groups in parent-reported exacerbations, however this did not persist (71). Morton et al. reported a difference between study groups in OCS course and hospital admission event rates over the study period as shown in *Table 3-5* (69). Foster et al. reported an unadjusted difference between patients in the EMD groups *vs.* non-EMD groups experiencing severe exacerbation (measured by OCS courses) over the study period (11% *vs.* 28%, p=0.013). The adjusted value, however, was not statistically significant (p=0.06) (68).

Three studies found a significant difference in asthma morbidity over the course of the follow-up period (see also *Table 3-5*). The first found a significant and clinically meaningful difference in both asthma morbidity score and C-ACT™ between intervention and control arms, although C-ACT™ plateaued at two months (71). Two others found significant and clinically meaningful improvements in reported asthma control across the study population over the course of the study, but no difference between control and intervention arms (68, 69).

Several studies looked at reliever use as an outcome measure (69, 71, 100, 156), although only Chan et al. and Onyirimba et al. measured this objectively using EMDs (*Table 3-5*). Chan et

al. reported a significant difference in the median percentage of days of reliever use between groups over the study period (71); however, this did not have a significant interaction with time. Onyirimba et al. found no significant difference in reliever use between groups (100).

In children, all three studies reporting baseline FEV_1 (69, 71, 156) showed an overall improvement in FEV_1 across their study populations but no significant differences, including in degree of improvement in FEV_1, between intervention and control groups. Of the four adult studies reporting percentage predicted FEV_1 at baseline, only Apter et al. reported an improvement in FEV_1 in a post-hoc sub-group analysis of participants with low baseline numeracy or AQLQ score (118).

Devices

Six studies reported problems with devices (68, 69, 71, 99, 118, 158) - generally participants not returning or damaging their devices (*Table 3-6*).

3.4.4. Study quality

Tables 3-7 and *3-8* present an evaluation of study quality for this review. Only three studies (68, 69, 71) reported in all areas considered. One study (71) was judged to have a low/intermediate risk of bias in all of the areas considered. The

main areas of concern were blinding, loss to follow-up and device reliability. Also of concern were the number of areas which were not reported (see *Tables 3-7* and *3-8*). Strengths of the studies included that they were randomised (with the exception of one study (157)) and that they were generally analysed in line with the original allocation intention, making their findings more applicable in a real-world setting.

Table 3-7: Review of EMD-based interventional studies – study quality (design)

Low risk of bias	Intermediate risk of bias	Higher risk of bias	Not applicable/not reported/unclear
• Randomised at person- level • Allocation concealment • Subject blinded to study hypothesis and EMD function • All of interventions/standard care/data collection/analysis blinded	• Randomised but not at person level • Subject blinded to hypothesis but not to EMD function; some subjects blinded to study hypothesis and/or EMD function • One or more (but not all) of interventions/standard care/data collection/analysis blinded	• Not randomised • No allocation concealment • Subject aware of both EMD function and study hypothesis • Study team unblinded to all of interventions/standard care/data collection/analysis blinded	

1st Author	Randomisation	Allocation Concealment	Blinding - Subject (hypothesis and/or EMD Function)	Blinding - Intervention Delivery and/or Data Collection
Apter(118)	Yes	Not reported	Partial	Not reported
Burgess (156)	Yes	Yes - sealed envelope	Unblinded	Partial - Control adherence blinded.
Chan (71)	Yes	Yes - sealed envelope	Full	Partial - automated intervention delivery, data collection not reported.
Charles (67)	Yes	Yes - sealed envelope	Full	Partial - automated intervention delivery, data collection not reported, adherence download post-visits.
Foster (68)	Cluster-randomised	Yes - method not elucidated	Partial	Partial - GPs blinded to alternative interventions, telephone data collection blinded, other data collection automated or postal; analysis blinding not reported.
Kenyon (158, 160)	Yes	Not reported	Unclear	Not reported

1st Author	Randomisation	Allocation Concealment	Blinding - Subject (hypothesis and/or EMD Function)	Blinding - Intervention Delivery and/or Data Collection
Kuipers (157)	No	N/A	Partial	Partial - pharmacy staff have access to all EMD data but no mandatory interaction with controls until study end; each pharmacy allocated to CARAT or no CARAT.
Morton (69)	Yes	Yes - independent code holder	Unblinded	Partial - control group clinicians blinded to adherence data when delivering clinical care.
Onyirimba (100)	Yes	Not reported	Partial	Partial - standard care delivery blinded, clinicians blinded to control group adherence data but may still deliver clinical care without reported blinding to study group.
Sulaiman(99)	Yes	Not reported	Unblinded	Partial - study team blinded to control group adherence data on data collection/intervention delivery visits. Automated data analysis, validation blinded.
Vasbinder (70)	Yes	Yes - method not elucidated	Unblinded	Not reported

Table 3-8: Review of EMD-based interventional studies – study quality (conduct and reporting)

Low risk of bias	Intermediate risk of bias	Higher risk of bias	Not applicable/not reported
• Power calculation reported • Baseline populations similar • ≤10% dropout rate • Intention to treat analysis • Analysis powered to detect outcomes • ≤10% device failure rate	• Baseline populations differ, but this is reported • 10-15% dropout rate • Per-protocol analysis only • Analysis not powered to detect outcomes	• Baseline populations differ widely, not reported • >15% dropout rate • >10% device failure rate	

1st Author	Power Calculation Reported	Baseline Differences Reported	Percentage Completion	Intention to Treat Analysis	Powered to Detect Change in Adherence	Powered to Detect Change in Outcomes	Device Reliability
Apter(118)	Yes	None reported	Not reported	Yes	Not reported	N/A	>10% download failure
Burgess (156)	Yes	None reported	100%	Not reported	Yes	N/A	Not reported
Chan (71)	Yes	None reported	96.8%	Yes	Yes	Yes	<10% non- return (no failures)
Charles (67)	Yes	None reported	81.8%	Apparent per-protocol	No	N/A	Not reported
Foster (68)	Yes	Reported differences	71.7% GPs 90.2% patients	Yes	N/A	No	<10% data unavailable due to loss/failure once activated
Kenyon (158)	N/A	Reported differences	78%	Apparent per-protocol	N/A	N/A	>10% data unavailable
Kuipers (157)	Yes	Reported differences	85%	Not reported	Not explicit - apparent	Not explicit - apparent	Not reported
Morton (69)	Yes	None reported	85.6%	Yes	N/A	Yes	>10% data unavailable - loss/ forgotten/ damage
Onyirimba (100)	No	None reported	63.3%	Apparent per-protocol	N/A	N/A	Not reported
Sulaiman(99)	Yes	None reported	89.4%	Yes	Yes	N/A	<10% device failure rate
Vasbinder (70)	Yes	None reported	95.4%	Yes	No	N/A	Not reported

3.5. Discussion

Eleven studies using EMD-based interventions with the aim of improving adherence and clinical outcomes were included in this review. Nine studies showed evidence of improved adherence; however, only two showed meaningful improvement in asthma-related outcomes when adjusted for baseline factors. This is in keeping with current evidence which suggests that EMD-based interventions do improve adherence but only inconsistently impact on clinical outcomes (46, 161). Note is made of how different the studies are in design, recruited population samples and interventions employed.

3.5.1. The impact of study population selection on study outcomes

Whilst the studies reviewed do not represent a large cohort, there is a clear suggestion that interventions using EMDs are unlikely to carry clinically significant benefits at an individual level unless certain criteria are met. The two studies which did show improvements in clinical outcomes were both in children who had, on average, exacerbated at least once within the three months preceding recruitment (69, 71). Importantly, much of the literature linking asthma outcomes with adherence shows associations with exacerbation as defined by OCS use, emergency department (ED) visits and hospitalisation (30-32).

Another distinguishing factor of these two studies was the absence of the fixed airflow obstruction (FEV_1 <80%) more commonly seen in adults who are at high risk of exacerbation. It is possible that this points to a comparatively lower burden of irreversible airway disease or a greater inflammatory component than in adults, perhaps rendering children more responsive to treatment with ICS than adults. It is also possible that this points to a greater behavioural component than in adults who may suffer more from intrinsic disease severity. If this were the case, exacerbations in these children may be more amenable to behavioural intervention.

Appropriateness of baseline ICS dose should also be considered. Four of the studies in this review suggested that their participant population may have been over-treated at baseline (67, 68, 70, 100). In theory, this could mask potential clinical benefits where a critical threshold for dose response has already been superseded despite a lower frequency of inhaler usage. Notably, however, studies linking adherence to outcomes have not checked the appropriateness of baseline prescription and therefore the impact of any blunting effect from overtreatment on clinical outcomes remains unclear (31, 33, 151).

Finally, there is a risk that participants are a self-selected group of motivated individuals. The three studies reporting baseline

adherence reported rates either at the higher end or above the higher end of the literature for adherence levels in asthma (50, 118, 157). This is in keeping with the high population estimate found in *Chapter 2*. There are broader implications for such selection bias. Although it is unlikely that people with asthma taking 64% of their prescribed ICS dose (see *Chapter 2*) would be receiving the full benefit of their inhalers (32), it may be that a small improvement in adherence does not lead to significant measurable clinical response in the 6-12 month durations employed by most interventional studies. Thus, it is possible that in the studies with high baseline adherence and other studies with relatively high rates of adherence in the control group at study end (67, 99), any gains in treatment effect from the intervention have been masked.

If real-world adherence is known to be poor and studies are potentially selecting for better adherence (162), this may explain in part why over a decade of interventional studies presented in this chapter have not seen consistent clinical improvements in outcomes. Thus, it may be that future RCTs attempting to show a change in clinical outcomes need to enrich for poor adherence in their population. This will involve finding innovative ways of engaging individuals who do not normally

engage with research but who stand to benefit the most from such interventions.

3.5.2. Electronic monitoring devices

Although less disparate than the EMD solutions noted in the previous chapter, there are again differences in the EMDs used, including more overt generational differences within the same brands. Points of variation included levels of validity and device capabilities (already discussed in depth in *Chapter 2*).

EMDs used in the studies reviewed varied from validated, commercially available platforms to devices designed by local study teams. Failure rates were generally low where reported, in contrast to the rates reported in the wider literature (see *Chapter 2*). Use of a validated, reliable EMD is clearly essential to this area of research and real-world practice will rely on these factors to establish trust and maintain objectivity on the part of the clinician.

One study found a disproportionate number of damaged devices returned by their intervention group (69). This highlights the possibility of a group that may be particularly resistant to engaging with EMD-based interventions. Such a group may require further characterisation in order for EMD researchers to be able to design effective interventions beyond what is offered

to the whole cohort (see *Chapter 6*). Malfunction, damage and loss of devices risk rendering EMDs useless if neither clinicians nor patients trust them (their value lies in the reliability and objectivity of the data they provide and in low loss/damage rates). Having uncompromising quality standards in the former case and understanding the motivating factors for the latter will be important if a large clinical study is to be viable, but also if these devices are to be used in routine clinical practice.

Whilst EMDs remain the best objective markers of temporal adherence available, this still does not guarantee drug delivery. Poor drug delivery may be intentional (known as dose dumping (69, 99)) and easily detectable by EMDs as multiple doses dumped at once, but harder to detect if spaced out at prescribed intervals or the result of poor inhaler technique. Indeed, in an observational study trialling their INCA device, Sulaiman et al. found that only 21 of 103 participants used their inhaler both correctly and in a timely manner. They further reported that, of 60 possible doses per month, although 82% were attempted, only 57% were actually taken correctly (99). This may well be even lower in a real-world population.

Only two studies (157, 158) reported the use of an app. Other studies generally involved the study team downloading information directly. In introducing these devices for real world

use, an alternative means to hard data download should be considered to limit resource impact on an already stretched clinical service. Alternative means of data download could also permit time for data to be converted into a format that is clinically meaningful.

3.5.3. Study intervention

Unlike drug trials that test a single chemical substance, behavioural studies can be difficult to evaluate as a group because of varying interventions and methodology. Particularly challenging is identifying how to control these studies.

Methods of participant blinding in this review included blinding control participants to their own adherence data, blinding all participants to the full study hypothesis (100, 118) and even covert monitoring (67, 68, 71). Covert monitoring or blinding participants to the EMD's full function may particularly help to reduce the impact of the knowledge of being watched i.e. the Hawthorne effect (143, 155). This may allow for the observation of behaviours that may not otherwise be reported. Patel et al., for example, in their covertly monitored study, found surprising levels of SABA overuse (95, 107). However, covert monitoring is accompanied by ethical issues requiring careful consideration. These include the process of obtaining informed consent and

management of patients who go on to use their inhalers in a mode indicative of a real-time medical emergency.

In the studies examined, there were varying applications of what was termed 'standard' or 'usual' care. These differences in control groups make comparison between studies challenging and may lead to an underestimation of the true effect of EMD-based adherence interventions. Innovative intervention design, on the other hand, is needed. It should be noted that, on the whole, adherence benefit has been seen in this review across a range of interventions from simple to complex, suggesting that at least for adherence, the benefits of EMD-based interventions exists regardless of the nature of the intervention.

Not all studies incorporated real-time automated reminders, which primarily target unintentional non-adherence. This may not be an essential component of such a function. Those that did and reported adherence over time all reported decay in adherence gains (67, 68, 71, 157). Speculatively, this may relate to a tolerance - or perhaps rather growing intolerance - of the reminder function, such that the positive effect initially seen is lost. Furthermore, with the exception of only two studies (68, 118), studies showing a decline in adherence in the intervention group did not incorporate any feedback on EMD use (67, 70, 71) whereas all of the studies reporting

maintenance of adherence gains did (69, 99, 100, 156, 157). This may indicate that clinician interaction in addition to technology is important, perhaps reinforcing the idea that the participant is being monitored. This sense of being observed may have otherwise worn off over time. The clinician interaction may separately be important due to the ability to personalise advice to users.

It is worth noting that neither study using a primarily behavioural strategy found improved adherence or outcomes as a result (68, 118). Other review findings suggest that tailored behavioural management interventions can be effective in improving objectively measured adherence (46), but warn that there is little evidence to suggest such strategies are more effective than 'simple' interventions (46). In both research and the real world, more complex interventions will be associated with increased training needs and time to deliver, consequently reducing external validity. Foster et al., for example, discussed difficulties providing training and standardising delivery with their study design.

It is possible that the interventions included in this review did not have long enough to translate into significant clinical outcomes. Indeed, the exacerbation benefits in the study by Morton et al. became marked in the second six month period of

their twelve-month study (69). Whilst running studies for a year or more would undoubtedly be costly, a positive result may be more generalizable. A negative result in this setting could cast serious doubt on the value of EMDs for improving real world outcomes in asthma and on their future in the areas of behaviour change and self-management in asthma.

Finally, free inhaler provision may have artificially inflated baseline adherence compared to a real-world situation. In several studies, this unintentional adherence barrier was removed in addition to the use of EMDs (67, 68, 100, 118).

3.5.4. Study quality

Quality measurement in this field has often relied on a standard set of expectations (114), however these do not recognise features unique to EMD-based interventions. Increasingly, truly covert measurement is becoming logistically challenging, with participants having easier access to external information than thirty years ago. Additionally, device reliability forms an essential part of critical evaluation, but is an aspect not normally considered. *Chapter 2* presents a concerted effort to adapt a widely recognised meter, the Cochrane quality score, for use in electronic adherence. This chapter presents only essential considerations, separating study blinding and covert monitoring as well as considering device reliability.

That no study in this review is completely free of concern in this review demonstrates how challenging study design is in this field, particularly when judged without consideration of the unique aspects of technology-based interventions. If a useful evidence base in this area is to be built, a more considered approach to study quality considerations will be needed. However, this must not preclude rigorous design, conduct and evaluation.

3.5.5. Future applications

This review's findings, although specific to the role of EMDs in improving adherence and clinical outcomes in asthma, are in line with existing literature that questions whether adherence interventions in asthma do actually improve clinical outcomes. That study design is likely to play a significant role in this lack of impact is borne out by the fact a 2003 review found less accurate measures may have led to an underestimation of the impact of interventions on adherence (162). The increased accuracy of electronic monitoring over other measures of adherence has moved the field forward such that it can be accepted that EMD-based interventions *do* impact adherence. It may be that similar attention to other aspects of study design in the context of such rapidly evolving technology may narrow

the gap between adherence and clinical outcomes seen in the current evidence.

Findings from this review suggest some basic considerations for future research in this field. These are summarised in *Table 3-9* (below). Finally, where participants have evidence of disengagement (e.g. device loss, difficulty organising follow-up appointments), researchers should attempt to assess the reasons why as this may be important for future clinical application.

Table 3-9: Review of EMD-based interventional studies – considerations for future study design

Overall study design	1. Longer term studies (*i.e.* ≥ 12 months). 2. Studies should be adequately powered to detect changes in **both** adherence and outcomes. 3. Consider pragmatic, real-world study design that is primarily delivered by the usual care team with study requirements delivered as remotely as possible to minimise risk of bias and maximise generalisability. 4. Baseline objective adherence should be measured, either using prescription data or a run-in period using the EMDs, possibly both as run-in electronically monitored adherence is likely to be subject to Hawthorne effect.
The population	1. Studies should enrich for participants who have had a recent exacerbation. This is the group with the most evidence at present for clinical outcomes. 2. Study designs should find innovative ways to engage potential participants with baseline poor adherence, bearing in mind the consideration that studies by their nature select participants who are likely to have a higher adherence than seen in the general population. Consider that individuals who have traditionally been difficult to engaged may also have more specific attitudes and behavioural needs that will need to be elicited and may require more complex interventions to address. 3. Consider subgroup analysis of individuals more likely to be corticosteroid-responsive (e.g. known eosinophilia) as a subgroup for clinical outcomes.
The intervention	1. EMD devices should be selected, not only based on their own capabilities, but on the basis of the inhaler device they fit to, considering (where possible) factors such as a participant's inhaler preferences. 2. Reliability, not just of a device brand, but also of specific models, must be an essential consideration in EMD selection. 3. Inhalation quality/technique detection/assessment should be measured in future studies to assess whether this is the cause of the gap between improved adherence and improved outcomes. 4. Studies should separate different behavioural components of the

	intervention: a. EMD + reminder b. EMD + feedback c. EMD + reminder + feedback. 5. More evidence is needed on evidence-based but easily deliverable behavioural interventions.
Outcomes	1. Any study assessing the effect of EMDs on adherence should measure at a minimum standardised markers of severe exacerbation and ideally also FEV_1. If possible to measure eosinophilia, or a surrogate marker for this, with minimal discomfort and inconvenience to the patient, this should be done as well. 2. A standardised measure of symptom control such as the ACT™ or ACQ should be used. Also consider objective SABA monitoring to support this. 3. Patient-related outcome measures which impact on adherence such as inhaler satisfaction should also be assessed.

Improving asthma treatment using inhaler technology

This thesis later presents a pilot study using and EMD-based intervention (see *Chapter 5*). The following considerations were incorporated into its design:

1. **Pragmatic, real-world study design**: Participants' usual care was conducted by their own clinicians rather than the study team. Adherence reports, where appropriate, were sent to participant's own clinicians to decide on appropriate interventions. There was no official study drug – participants were enrolled if their inhaler was compatible and formulation switches to enable this were avoided as much as possible. Study contact was remote during the middle months of the study to minimise study team contact.

2. **Enriched for exacerbation**: self-reported exacerbation within the preceding 12 months was a study eligibility criterion.
3. **Recording of phenotyping data**: whilst this pilot study was small and not designed for subgroup analysis, data on the presence or absence of historical eosinophilia, raised fractional exhaled nitric oxide (F_ENO) and airflow obstruction were recorded.
4. **EMD selection**: the study selected the Smartinhaler™ platform as a brand which had been tested in multiple studies and had good validation data, including for the generation of models used.
5. **Intervention selection**: the study was designed to separate the effect of feedback from other measures as its primary intervention.
6. **Outcome measures**: the study measured severe exacerbations, FEV_1, ACT™ and AQLQ as well as electronically-monitored SABA use as clinically relevant, standardised and comparable outcome measures.

Due to its nature as a pilot study, it was not designed to be fully powered. Furthermore, due to limitations regarding available devices available at the time, technique assessment was not a feature of the EMDs chosen. Finally, the study incorporated a

qualitative aspect which aimed to explore user perspectives in more detail given the relative novelty of this field.

3.6. Conclusion

EMDs may be an important tool in combatting the results of poor adherence to inhaled medications in asthma; however, studies to date have shown limited benefit in both subjective and objective clinical outcomes. This should serve as an alert to both the research community and relevant stakeholders, stimulating more considered research in this field.

Studies should be designed to be rapidly deliverable, adapting to changes in technology, widely generalizable and with relevant outcome measures. Designs should give careful thought as to who will benefit from these interventions and precisely which interventions they are likely to benefit from. This will create an opportunity for risk reduction and allow the identification of the subgroup of patients with truly treatment-resistant asthma.

Chapter 4: Accuracy and reliability of Smartinhaler™ technology – experience from a feasibility study

4.1. Introduction

This thesis examines the rationale for the use of EMDs in clinical practice, prior study evidence, the gaps in that evidence and the ways in which those gaps might be filled. In 2017, the UK's National Institute for Health and Care Excellence (NICE) appraised the Smartinhaler™ system with a view to use in clinical practice (154). However, for these devices to translate readily into clinical practice, they must also be reliable and easy to use. For the pilot interventional study later presented in this thesis, the Smartinhaler™ system from Adherium (New Zealand) was used for both interventional and control groups. This was both due to investigator experience with the system (95, 96, 163, 164) and supportive validation data (163, 165, 166). A gap is noted in several studies reviewed in both *Chapter 2* and in *Chapter 3* of this thesis in reporting on device validity and failure. This is noted to be important in the interpretation of study results. Investigator experience of device reliability from the study is therefore presented in this chapter.

4.2. Aims and objectives

This chapter aimed to:

1. Review investigator-led validation data for the Smartinhaler™ system.
2. Present methodology adapted from validation studies.
3. Present device testing results from a pilot study of adherence.

4.3. Literature review

Six investigator-led papers published between 2006 and 2016 were found to describe the use of the Smartinhaler™ system (163, 165-169). They are presented in *Table 4-1*. When judged on actuations, the Smartinhaler™ system consistently provided a greater than 90% accuracy in recording inhaler actuation events, where accuracy was defined as number of actuations correctly recorded (see *Table 4-1*). However three of the six papers suggest a spread of erroneous recording across devices rather than concentrated in a small number of faulty devices (166-168). Thus, whilst it appears that a high level of data accuracy can be expected from the system, it is possible multiple individual devices may mis-record events on occasion.

Table 4-1: Literature review of device testing

Paper (First author, year)	**Device**	**Study Design**	**Device accuracy**	**Author comments and recommendations**
Burgess, 2006 (167)	Smartinhaler™	Study 1: 30 days, two puffs twice daily Ten Smartinhaler™ devices. Canister weight before and after each pair of actuations Date and time manually recorded, recorded by the Smartinhaler™ and recorded by the Doser CT manually entered onto spreadsheet for comparison. Study 2: Single day Six Smartinhaler™ devices had 30 actuations in rapid succession. Data downloaded was compared to known number of actuations.	**By device:** 5/10 devices 100% accurate **By total actuations:** 111/120 (92.5%) **Rapid actuations:** All devices record 30 actuations but time stamp all with first actuation time.	Five devices missed first or second dose only. This appears related to how firmly the canister has been inserted into the device. **Recommendation:** the canister should be actuated on insertion. **Note:** The time stamp is repeated when actuations are in rapid succession.
Foster, 2012 (168)	SmartTrack™	Study 1: Single day, 10 devices. Test markers of device functionality including clock accuracy, accuracy of x3 actuation logs and insertion/removal logs, and reminder functions. Study 2: Devices passing *Study 1* testing. Two days of two puffs twice daily, followed by 30 actuations in rapid succession. Date/time recorded in a log as was dose counter reading before and after each pair of actuations and before and after the rapid succession routine. Data downloaded compared. Study 3: Devices passing *Studies 1 & 2* testing. Seven days patient field testing.	**By device:** 6/10 devices 100% 2/10 devices minor issues only **By total actuations:** Study 2: 98.8% Study 3: 97% dose counter agreement, 95.6% paper diary agreement	One device failed Study 1, not logging any events. Three devices showed minor issues in Study 2. One device had 2/38 actuations differing from diary times by up to 35s, although it was noted this was likely due to human error. Two devices recorded spurious events – one on device inhaler insertion, the other duplicating a single event. One device failed Study 2 with electrical circuit failure. There was no evidence of missed actuations. Two devices recorded extra actuations on insertion of the MDI. At seven days, median battery life was ¾ bars.

Paper (First author, year)	Device	Study Design	Device accuracy	Author comments and recommendations
Foster, 2012 (168)				**Recommendations:** *"Routine QC testing prior to dispensing and after return remains essential for any electronic monitoring device, in both research and clinical practice."* The authors also suggest expectation of a 20% malfunction rate and provision to therefor be mad for purchase of 10-20% extra devices to replace device failures. Remove from analysis any actuations with same stamp as inhaler insertion. Advise three attempts at upload as routine. Warn that in reminder mode, device may require more frequent charging.
Patel, 2012 (169)	Smartinhaler™ Tracker	Testing at 0, 8, 16 and 24 weeks. <u>Study 1:</u> 2 days: 2 actuations 10-20s apart repeated at least 2 hours later. <u>Study 2:</u> Single day: 2 actuations 10-20s apart repeated at least 2 hours later. <u>Study 3:</u> Single day: 8 actuations 10-20s apart repeated on 2 other occasions on the same day <u>General function:</u> battery charge, data retention, spurious log, clock accuracy etc.	**By device:** 20/22 (90.9%) **By total actuations:** 2170/2176 (99.7%) number of actuations 2160/2176 (99.3%) accurate date/time stamp	All missed actuations were during low-use testing. Some extra actuations were related to computer connection. A mean time drift of five weeks was noted over the testing period. Battery charge at 24 weeks was full charge. **Recommendation**: Pre-study screening checks to screen for faulty devices are require prior to patient use. Data recorded on study visit days could be removed from analysis to prevent inclusion of spurious connection events and dose dumping.

Paper (First author, year)	Device	Study Design	Device accuracy	Author comments and recommendations
Patel, 2013 (163)	Smartinhaler™ Tracker	24 week RCT – visits at 3, 10, 17 and 24 weeks <u>Pre-study protocol:</u> 1. Monitor clock synchronised 2. Two actuations, simultaneous paper diary log 3. A further two actuations two hours later, simultaneous paper diary log 4. Accuracy check and all failed devices returned <u>Within-study protocol:</u> 1. Check 48h before next study visit. 2. TEST function selected (monitor reset by software) 3. Investigators prompted to actuate device twice 4. Software checked monitor and computer clock, date/time stamp, battery charge. If device failed any element, software prompts for return to manufacturer. <u>Within-study data protocol:</u> 1. Investigator preview of data 2. Investigator upload of data 3. Time discrepancy>=15 minutes between monitor and computer clock prompts identification of device for reference RE data and return to manufacturer	**By device:** 2678/2728 (98.2%) monitors pass pre-study checks 2498/2642 dispensed monitors (94.5%) and /2549 returned monitors (98.0%) had complete data.	Of 50 devices failing pre-study checks, 26 missed actuations, 20 recorded extra actuations, four had structural faults. 15 were repaired and used subsequently. Of 76 devices failing within-study checks, 33 failed due to battery, 25 due to MDI nozzle blockage, 12 had erroneous actuation records and four duplicated actuation records. Of 51 monitors failing data upload checks, the majority showed evidence of moisture damage. **Recommendation:** Smartinhaler™ Tracker is highly reliable. Extensive pre- and within-trial processes should be implemented. Incorporated systems may assist with this. Bench testing and canister weighing should also be considered to establish validity.

Paper (First author, year)	Device	Study Design	Device accuracy	Author comments and recommendations
Pilcher, 2015 (166)	SmartTurbo™	12 week bench testing (testing days 0, 5, 6, 7, 8, 9, 14, 21, 28, 56, 84 Low use pattern: Two actuations up to two minutes apart, no use for >=1.5 hrs, 2 actuations up to 15 minutes apart High use pattern: 8 actuations within 5 minutes, no use for >=1.5hrs, 8 actuations within 5 minutes	**By devices:** 15/20 (75%) record actuation events with 100% accuracy (i.e. no missed or spurious events). 18/20 record all insertion/removal events accurately. **By actuations:** 2796/2800 (99.9%) accurately recorded actuations	Issues with spurious actuations and clock found to be central programme algorithmic issues rather than device issues. **Recommendation:** The SmartTurbo is an accurate device. Close cooperation with the manufacturer is recommended. Studies should allow for time drift. Clear education regarding Turbohaler use essential. **Note:** Algorithms still in development
Pilcher, 2016 (165)	SmartTouch™	10 weeks Ventolin Pre-study simulation: Two actuations separated by 10-20s, at least 15 minute break, two further actuations separated by 10-20s Within-study simulation: MDI replaced, two actuations 10-20s apart. Failure = missed actuation, spurious actuation, battery light not green	**By device:** 18/20 (90%) record actuation events with 100% accuracy (i.e. no missed or spurious events). One device missed one insertion and one removal event. **By actuations:** 2558/2560 (99.9%)	All devices passed initial study, within-study and battery checks. **Recommendation:** The SmartTouch™ is an accurate device for measuring actuations over a 10 week period. Initial study and within-study checks should be performed Participants and investigators should be trained as to correct use Allow for time drift

This was also demonstrated in Pilcher's most recent evaluation of the SmartTouch™ device where all devices passed basic pre-study and within-study simulated checks, but two actuation events went unrecorded (165). However, whilst occasional mis-recorded events occurred, this did not appear to demonstrate systemic issues. As Burgess et al. (167) showed, early missed doses did not necessarily go on to signal general device failure and could be explained.

The studies highlighted particular device idiosyncrasies for consideration. One, for example, suggested that canisters be inserted with enough pressure to generate an actuation to confirm good fit (167) and another highlighted the importance of the inhaler technique with regards to turns in the Turbohaler (166). A third highlighted the importance of thumb placement (at the base of the device) for the SmartTouch™ (165). Several authors caution to expect a clock drift over several weeks of usage. For earlier devices, the manufacturer gave an estimate of 15 minutes of clock drift over 12 months (163). For newer devices, this is reported as 60 minutes over 12 months (165).

In summary the Smartinhaler™ system has consistently been validated as accurate with a caution around the unpredictability of mis-recorded events. These occasional mis-recorded events do not appear to represent systemic malfunction. Study authors

consistently advised pre-study and within-study checks and earlier authors advocated post-study testing as well. Pilcher et al., (166) further advocated for close involvement of the manufacturers as part of the quality assurance process. Exclusion of data around inhaler insertion and visit days is also suggested to improve the quality of data analysed.

4.4. Methods

Methodology was derived from three of the studies already discussed (163, 165, 169). The initial decision was taken to perform pre-study checks and within-study checks as described; however, due to ongoing issues as the study unfolded, post-study testing was introduced on a batch-by-batch basis on all devices which had been provided to participants. Furthermore, a rapid device check for devices that had their initial testing more than six weeks in advance was instituted. Thus, whilst pre-study and within-study protocols were determined *a-priori*, pre-dispensing and post-study checks were implemented and adapted during the course of the study.

4.4.1. Devices

The Smartinhaler™ system (Adherium, New Zealand), rebranded Hailie™ during the study, was used. As the EMDs were designed to be inhaler-specific, SmartTouch™ devices to

fit Seretide (fluticasone/salmeterol), Fostair (beclomethasone/formoterol), Ventolin (salbutamol) and Salamol (salbutamol) were obtained. During the study, the decision to include the Symbicort (budesonide/formoterol) and Bricanyl (terbutaline) Turbohalers was taken and the SmartTurbo™ devices to fit these were included in the study protocol. The devices attached to their respective inhaler devices as illustrated below in *Figure 4-1* and *Figure 4-2*.

Figure 4-1: SmartTouch™ device

Figure 4-2: SmartTurbo™ device used in the study, an earlier version of the Hailie® sensor for use with SYMBICORT® Turbuhaler® inhaler

Actuations were detected by the devices using a small electromechanical sensor. In the SmartTouch™, this was situated at the base of the device and so detected depression of the inhaler (165). The SmartTurbo™ used a torque

mechanism to detect completed Turbohaler turns (166). These detected actuations were transmitted via Bluetooth® to an associated mobile phone application (app) which in turn transmitted this via Wi-Fi to a cloud-based server. The events could therefore theoretically be seen in real-time, so long as the device and Bluetooth® device were in close enough proximity and Bluetooth® and Wi-Fi were activated (*Figure 4-3*).

Figure 4-3: Example of the Hailie platform

© Adherium

Two versions of the Smartinhaler™ app were available. In the full version, users were able to see their prescribed doses and their data. This app version was provided to the intervention group as part of their feedback. In the control version of the app (*"Smartinhaler™ Lite"*), users could see only their device battery and synchronisation status. This was the app version provided to the study control group. There was also potential to download event logs via universal serial bus (USB) using dedicated software ("*Connection Centre*").

4.4.2. Pre-study testing

All devices were checked by a trained investigator prior to being dispensed as follows:

1. A unique test ID was created for each device.
2. A battery check was conducted by pressing the button located on the side of the SmartTouch™ or SmartTurbo™ device. Devices passed this if the LED flashed green.
3. The device was then connected to the mobile app via Bluetooth.
4. Devices were then fitted to the appropriate inhaler (dummy or test). The time of fitting (as per the computer clock) was recorded to the second on a purpose-designed electronic spreadsheet log.
5. Two actuations about 20 seconds apart were discharged. The time of each actuation was recorded onto the spreadsheet.
6. After a gap of around 15 minutes, two further actuations about 20 seconds apart were discharged. The time of each actuation was recorded on the spreadsheet.
7. The inhaler was removed from the device and time of removal recorded on the spreadsheet.

8. The application was then changed over to the control group (*Smartinhaler™ Lite)* mode via the web-link.
9. The whole test process (steps 4-7) were repeated in the *Lite* mode with a check that no actuation data would be visible.
10. Electronic log records were checked to see whether there was a match in:
    a. Insertion times
    b. Actuation times
    c. Removal times

    There was a column for recording of missed or spurious events and comments to include suspicion of human error. To accommodate for clock drift, lack of synchrony between computer and mobile phone clocks and human error, delays of up to 60 seconds between investigator-recorded times and the device log were accepted.

11. A final battery check from both the web link (≥3 bars) and the device (green LED) was performed.
12. Finally, the device was checked for ability to connect to the USB download PC software (Connection Centre).

Devices were declared for participant issue if the following conditions were met:

1. Battery checks were passed (≥3 bars and green LED)
2. All insertion and removal logs were recorded within 60 seconds of the manual times entered on the electronic log
3. No actuation events were missed and all actuation events recorded were within 60 seconds of the manually recorded times on the electronic log
4. No spurious actuation events were recorded
5. There were no visible data in the *Lite* half of the testing protocol
6. The device connected to the download software

Devices which did not meet these criteria were re-tested, in case of there being clear, remediable explanations for the original test failure. Re-test devices were generally given new unique test IDs. Where devices failed the re-test or passed the re-test with no potential reasons for having failed in the first place, liaison with the manufacturer took place and they were removed from circulation.

4.4.3. Immediate pre-dispensing checks

During the course of the study, where the duration between the original pre-trial testing and dispensing of the devices was prolonged (generally more than six weeks), a rapid pre-dispensing check was conducted as follows:

1. The same test ID as on the last successful pre-trial test (or a new test ID accounting for testing on the day of issue) was used in full mobile app mode.
2. A dummy or pre-specified test inhaler was inserted into the device and the date and time entered manually on the electronic log.
3. Two actuations about 20 seconds apart were discharged and the time for each manually entered on the electronic log.
4. The inhaler was removed and the time of removal manually entered on the electronic log.
5. The battery on the device was checked as was the battery status on the online web-link.

Devices were marked for issue if:

1. Battery checks were passed (≥3 bars and green LED)
2. No actuation events were missed.

3. All actuation events recorded were within 60 seconds of the manually recorded times on the electronic log if the device had been synchronised with the mobile app prior to testing (clock drift was permitted if this had not occurred).
4. No spurious actuation events were recorded

4.4.4. Within-study testing

At approximately monthly intervals, simultaneous with participant data checks, the online web-link was accessed. Information was stored on the electronic spreadsheet log. The following information was logged:

1. Battery life
2. Insertion of an inhaler detected
3. Actuation detected
4. Date since last upload
5. Concerns/comments

Concerns and comments could include where there had been more the seven days since the last recorded upload, where on review of the data there were recurrent episodes of sporadic missed doses or sections where no actuations had been recorded, or where participants themselves had raised concerns in the intervening period.

4.4.5. Post-study testing

1. Devices were generally matched to their prior unique test ID or had a new ID created where the test and study ID were the same.
2. A battery check was conducted as in the pre-study tests.
3. The device was then synchronised with the mobile app via Bluetooth.
4. Devices were then fitted to the appropriate inhaler (dummy or test). The time of fitting (as per the computer clock) was recorded to the second on a purpose-designed electronic spreadsheet log.
5. Two actuations about 20 seconds apart were discharged. The time of each actuation was recorded onto the spreadsheet.
6. After a minimum gap of around 15 minutes, six further actuations about 20 seconds apart were discharged. The time of each actuation was recorded on the spreadsheet.
7. The inhaler was removed from the device and time of removal recorded on the spreadsheet.
8. Electronic log records were checked to see whether there was a match in:
    a. Insertion times

b. Actuation times

c. Removal times

As with pre-study testing, there was a column for recording of missed or spurious events and comments to include suspicion of human error. Delays of up to 60 seconds between investigator-recorded times and the device log were accepted. Longer delays were recorded and did not constitute a major fail, particularly if synchronisation with the mobile app occurred later in the testing process. Devices were then linked to the *Connection Centre* software and, where there was a discrepancy between previously uploaded logs and the USB download logs, additional logs were downloaded.

4.4.6. Further considerations

During post-study testing, it became clear that certain devices were particularly liable to miss logs where there was a short period of time between insertion/removal events and actuation events. In subsequent tests, a gap of 60 seconds was left between insertion or removal and actuations to reduce the risk of missed actuations.

4.4.7. Analysis

Data were entered directly onto an electronic spreadsheet log (Microsoft Excel, 2016). This was uploaded into Stata (Stata

version 15, Statacorp) for further analysis. Numbers of devices which underwent pre-study testing as a proportion of total devices obtained and which passed pre-study testing as a proportion of total devices tested were calculated. Proportions of devices which failed pre-study testing were also calculated for the batches received, different device types and for each study group. Non-parametric tests (Wilcoxon's Rank Sum) were used to assess whether the batch, device type or study group were associated with an increased likelihood of device failure pre- and/or post-study use.

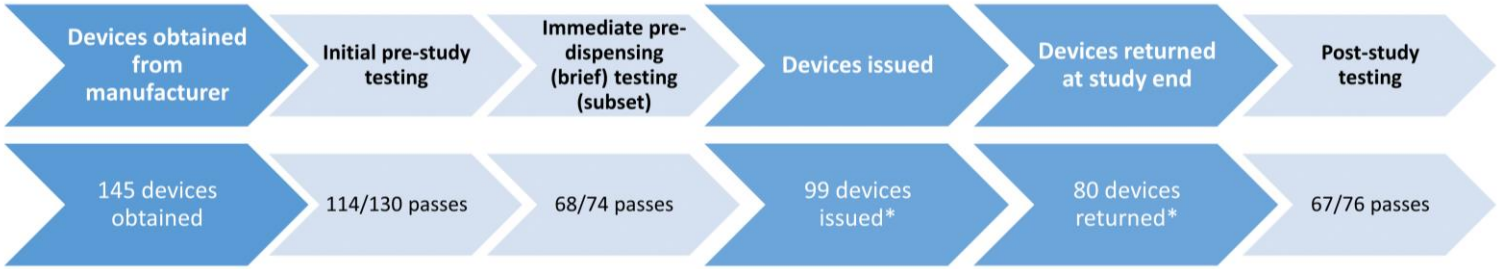
Numbers of devices which were returned as a proportion of those issued and of those which passed post-study testing as a proportion of those returned were also calculated. Non-parametric tests were again used to assess whether devices which required re-testing prior to their study use were more likely to fail post-study testing than those which passed pre-study testing first time. Similarly, non-parametric tests were also used to assess whether devices passing pre-study testing with minor issues (such as clock discrepancies) were more likely to fail post-study testing than those which did not pass with minor issues.

4.5. Results

4.5.1. Pre-study testing

Over the study period, 145 SmartTouch and SmartTurbo devices were obtained from the manufacturer (see *Figure 4-4*). Of these, 130 devices underwent pre-study testing. *Table 4-2* details the results of this. Of 130 devices which were tested prior to issue, 82 (63%) passed first time with no issues, 23 (18%) passed on re-testing (the reasons for these are detailed in *Table 4-3*) and nine (7%) passed with minor issues *(Table 4-4)* giving a total of 114 (88%) devices which passed pre-study testing. Of 2726 events carried out in pre-study testing, only 169 were missed, giving a proportion of 94% events correctly detected by tested devices.

Figure 4-4: Testing procedures and device flow



**single device issued twice to separate participants*

Devices requiring re-testing prior to pre-study testing pass

With regards to devices which passed on re-testing *(Table 4-3)*, devices were re-tested following initial test failure if there did not appear to be an intrinsic device reason for failure (i.e. human error may have been implicated in the testing failure). In three devices which were returned for a second round of testing after having been reviewed by the manufacturer, the battery had not been fully charged prior to re-testing. In five devices, a clock discrepancy (i.e. the electronic time stamp was more than 60 seconds out compared with the investigator-recorded time stamp) was probably due to the device not having been synchronised to the mobile phone app prior to testing. Where this was the case, synching would automatically occur later in the test such that later timestamps did match up. One device was unable to be synchronised to the mobile phone app.

Table 4-2: Device flow with pre-study and post-study testing results

Device (by compatible inhaler)	**Total tested, *n=130* (% total obtained, *n=145*)**	**Passed pre-testing, *n=114* (% total tested, *n=130*)**	**Issued to participant, *n=100***	**Returned to site, *n=81* (% issued, *n=100*)**	**Unable to post-test, due to battery *n=5***	**Passed post-testing, *n=67* (% returned, *n=81*)**
Bricanyl	4 (100)	4 (100)	2	2 (100)	1	0 (0)
Fostair	39 (85)	33 (85)	32	25 (78)		17 (68)
Salamol	14 (100)	13 (93)	10	8 (80)		8 (100)
Seretide	13 (76)	9 (69)	5*	5* (100)	1**	4** (80)
Symbicort	13 (81)	13 (100)	13	10 (77)		10 (100)
Ventolin	47 (98)	42 (89)	38	31 (82)	3	28 (90)
Total	130 (90)	114 (88)	100	81 (81)	5	67 (83)

*701210 was issued twice **701210 passed the first post-study test and was unable to be tested for the second post-study test due to battery failure

Table 4-3: Causes of failure for devices which passed on re-testing

Fail category	**Number of devices, *n=23****	**Issued to participant, *n=20***	**Returned to site, *n=14* (% issued, *n=20*)**	**Passed post-testing, *n=12* (% returned, *n=14*)**
Battery not fully charged prior to testing	3	3	2 (67)	1 (50)
Clock fail (>60 second time discrepancy)	5	5	3 (60)	3 (100)
Unable to connect with app	1	0	-	-
Missed initial installation	4	3	1 (33)	1 (100)
Missed single actuation	11	10	8 (80)	7 (88)
Missed multiple actuations	3	3	3 (100)	2 (67)

*Some devices met more than one failure category

Table 4-4: Devices which passed with minor issues

Fail category	**Number of devices, *n=9* (% total passed, *n=114*)**	**Issued to participant, *n=9***	**Returned to site, *n=8* (% issued, *n=9*)**	**Passed post-testing, *n=6* (% returned, *n=8*)**
Battery at half-life	6 (5)	6	5 (83)	4 (80)
Clock fail (>60 second time discrepancy)	3 (3)	3	3 (100)	2 (67)
Total	9 (8)	9	8 (89)	6 (75)

Further into the study, it was noted that several devices had missed initial device fit events, removal events or actuation events immediately prior to or after these events on pre-study testing. It emerged that, because the electronic timestamp was often slightly delayed for device fit and removal events, there was overlap between these and actuation events. In subsequent testing, a 60 second gap was left before and after monitor fit and removal events; however prior to this, four devices failed initial testing due to missed device fit events and eleven devices failed due to single missed events.

Human error was another possible cause of isolated missed events (i.e. time of intended actuation was recorded without actuation taking place). Finally, three devices appeared to miss multiple actuation events, although this appeared to resolve on repeat testing.

In total, of 76 devices which were returned by participants and could be tested on their return after the study, 15 (20%) had experienced at least one test failure prior to issue. Initial failure did not appear to predict post-study failure however as 13% of devices which had experienced a test failure were found to fail following their return, compared with 11% of devices which had not had any test failures prior to issue ($p=0.84$).

Devices issued following a minor fail

Nine devices were issued following a minor test fail. In one batch of Ventolin devices, the battery on initial testing was noted to be at half-life. This was discussed with the manufacturer who reassured that they would last the duration of the study. Three devices had minor clock issues as discussed above. This was not detected prior to issue in one device, however the two devices where it was noted also underwent pre-visit checks and where the time stamp discrepancy was shown to be due to be human error in the test process.

In total, of the 76 devices tested following study use, seven had experienced minor fail in the test prior to issue. Of the seven, one device (14%) went on to fail post-testing compared with eight devices (12%) of devices which did not experience a minor fail. This difference was not statistically significant (p=0.83).

Failed devices by batch

Devices were ordered at various points in the study with the result that they were received in 11 separate batches. As most device failures appeared to occur in the earlier part of the study, failed devices were analysed by batch provided *(Table 4-5)*. There were no failures in the last five batches obtained. There

was an association between batch and the proportion of device failures (p=0.002).

Table 4-5: Device failures by batch obtained

Batch	1	2	3	4	5	6	7	8	9	10	11
Number of devices tested	34	1	7	11	9	21	7	27	5	7	1
Pre-study failures (%)	11 (32)	1 (100)	1 (14)	0 (0)	1 (11)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

4.5.2. Immediate pre-dispensing checks

Immediate pre-dispensing checks were carried out where either a significant period of time (four to six weeks) had elapsed between pre-study testing and the date they were due to be issued or because there was a minor issue (see *Table 4-4)* found in pre-study testing. The aim of pre-dispensing checks was to ensure that battery life was maintained and that devices were still able to record every actuation.

Seventy-four devices underwent pre-dispensing checks (including one which underwent pre-visit testing twice for issue to two separate participants). Of these, six (8%) failed testing and were not issued to participants. Five of these test fails were returned to the manufacturer for review.

4.5.3. Within-study replacements

Ninety-nine devices were issued to participants (one device was issued twice giving 100 device issues). Most participants were issued a single preventer device and a single reliever device; four participants who indicated at enrolment their use of multiple reliever devices were also provided with a second reliever device. Of devices issued, 22 devices were replaced before the end of the study period, 16 for possible malfunction (see *Table 4-6*). Three of these possibly malfunctioning devices were from control group participants (7% of control group devices) and 13 were from intervention participants (24% of intervention group devices).

Table 4-6: Reasons for replacing devices during the study

Event	**Number of devices, *n=22***
Suspected malfunction	16
Device loss	2
Change of inhaler regime	2
Incorrect device for inhaler	2

Of the 16 devices with a suspected malfunction, only three devices failed post-study testing – one fail due to battery failure and two fails due to failure to record actuations.

4.5.4. Post-study testing

Overall, of the 100 device issues, 19 devices were never returned (12 because of participant loss to follow-up and seven

because participants lost them). Five issues were unable to be tested due to confirmed or probable battery failure (one of these occurring during the study as described). Nine devices failed post-study testing outright and 67 issues passed testing *(Table 4-2)*. Thus of 76 returned devices that were suitable for testing, the device failure rate was 12%.

With regards to battery failure, devices were tested in batches and a few non-rechargeable devices drained before there was an opportunity to test them. In two Bricanyl-compatible devices, no actuations were recorded although the battery light showed green. One of these was tested at 356 days following original testing, the other at 501 days. Battery life expected was to be around 365 days for these devices. The latter device was therefore classified as a probable battery failure. The former device is likely to also be a battery failure but did not meet the 365-day cut-off.

When analysed by batch (eleven in total), participants received devices from all but the second batch (a single device which failed). There was no association between batch and likelihood of a device to fail post-study testing ($p=0.402$). This suggests that despite all pre-study device failures coming from devices supplied earlier in the study, earlier batches of devices which

passed testing and were issued to participants were no more likely to fail than later devices.

4.5.5. Manufacturer feedback

In total, 28 devices (19%) were returned to the manufacturer due to queries around their function. Sixteen of these devices had failed pre-study testing and never been issued, four had passed pre-study testing but were recalled by the manufacturer prior to being issued and eight had been issued to participants. Of the eight which had been issued to participants, five had passed post-study checks but had within-study concerns or had been recalled by the manufacturer. Formal feedback was obtained for 19 devices with informal feedback via email communication for the first batch of five Seretide-compatible devices (i.e. feedback for 86% of devices returned). This is detailed in *Table 4*-7.

Table 4-7: Outcome of manufacturer investigation for devices returned to them (includes issued devices)

Manufacturer investigation outcome	**Number of devices (% devices investigated), *n=24***
Device fault confirmed	16 (67)
Design fault	6 (25)
Liquid damage	1 (4)
Test process issue, no device fault	1 (4)
Total	**24 (100)**

Device faults primarily related to the first batch of Fostair-compatible and Seretide-compatible devices received. The Fostair-compatible devices were found to be too tight for the

inhaler leading to missed actuation logs. Similarly, email feedback with regards to the Seretide-compatible batch also suggested a problem with the device's plastic casing. Other device faults included problems with one device's optical reader leading to spurious installation/removal events device, a logged data duplication in another device and a fault found within a device component which was causing excessive battery drain.

Design faults on the other hand related to issues with the battery measure supplying an incorrect reading rather than any fault intrinsic to the hardware of the device in question. In another device, liquid damage was logged as occurring between the date of the last device test and issue to the participant, causing excessive battery drain. The device where a test process issue was identified highlighted an inadequate duration of time between installation/removal events and actuations. This had already been noted by the time the manufacturer feedback was received. Manufacturer feedback for devices used by participants is shown in *Table 4-8*.

Table 4-8: Outcome of manufacturer investigation for devices which had been issued, by Study ID

Study ID	**Outcome of manufacturer investigations, *n=8***
SIT001	Device fault (x2 devices)
SIT002	Device fault
SIT006	Device fault
SIT008	Device fault
SIT011	Battery measure fault
SIT016	Liquid damage
SIT017	Battery measure fault

4.5.6. Devices by group

The pilot study for which these devices were used divided participants into intervention (electronic monitoring device [EMD] + feedback including visible app data) and control (EMD, no feedback, no app data) groups. Eighteen control group participants were provided with 45 issues of 44 devices (a mean of 2.50 devices per participant). Eighteen intervention group had 55 devices issued (a mean of 3.06 devices per participant). Intervention group participants were more likely to be provided with devices that had suffered a minor fail in pre-study testing (i.e. one device was provided to a control group participant as opposed to eight devices which were provided to intervention group participants, p=0.032).

Devices by inhaler compatibility were distributed relatively evenly between the groups. Overall there were no differences in the inhalers used by the groups (p=0.972) and, when taken by the first device issue, exactly the same number of participants in each group had Fostair-compatible, Seretide-compatible and Symbicort-compatible devices *(Table 4-9)*.

Table 4-9: Inhaler compatible device by study group

Inhaler type	Intervention group (N=55), *n*	Control group (N=45), *n*
Fostair	12	12
Seretide	2	2
Symbicort	4	4

Most importantly, of the 76 devices which underwent post-study testing, 3 of 30 Group A (10%) and 6 of 46 Group B (13%) issues were found to fail and this difference was not statistically significant (p=0.688). The discrepancy between returned Group A and Group B devices is explained by the lower number issued to Group A participants (possibly due to replacements as discussed) but also by the lower number of Group A devices returned. Thirteen (29%) of Group A devices were not returned as opposed to six devices (10%) of Group B devices. This may in part be explained by the fact that five of the six participants lost to follow-up (accounting for 10 of the 19 devices not returned) were control group participants.

4.5.7. Fostair inhaler structure

During the period when the study was running, Chiesi, the manufacturer of the Fostair inhaler, amended the design of the inhaler to incorporate a dose-counter and stopped distributing older models of the non-dose-counter inhaler in the UK. This created a potential impact on reliability of the Fostair-compatible devices. Furthermore, almost all of the post-study device failures (89%) were from the Fostair-compatible devices. It was unknown whether participants used integrated dose-counter or non-dose-counter inhalers and this, in addition to the variability of Fostair device reliability across the batches,

makes it impossible to rule out that the change in inhaler design may have played a role in device reliability. Excluding the Fostair devices from the pre-study testing figures only slightly reduced the failure rate from 12% to 11%. Excluding them from the within-study testing figure more markedly reduced the device failure rate from 12% to 2%.

4.5.8. Testing procedure exceptions

During the study, there were some exceptions to the procedures detailed above. These are listed below.

1. A subgroup of devices appeared to have low battery (half-life) on initial wakening. This was discussed with the manufacturers and the study team was reassured that battery failure was not expected and so was adjusted on the testing protocol.
2. Due to factors in obtaining devices and rapidly booking appointments, device testing occasionally took place the day before or on the day of the baseline visit rather than 48 hours prior. This has been accounted for in data analysis by removing Day 0 from the data.
3. Devices were used in the study where they had failed testing more than once so long as they had subsequently passed testing. This was particularly the case where devices appeared to have a clear reason for failure e.g.

investigator error in synchronisation pre-test leading to apparent clock failure or low battery in rechargeable devices where testing had already taken place previously.

4. Testing took place more than six weeks prior to issue in two devices: 806033 issued to SIT034 43 days after testing and 708025 issued to SIT028 66 days after testing.

4.6. Discussion

4.6.1. Study findings

This study obtained 145 devices compatible with six different inhalers from the device manufacturer. One hundred and thirty were tested in accordance with adapted published testing protocols. Although 94% of device events were accurately captured, there was a pre-study failure rate of 12% (*n*=15) and a post-study failure rate of 12% (*n*=9). Minor problems with clock and battery did not seem to impact on within-study need for replacement or, more importantly, with device reliability as predicted by passing post-study testing. Most importantly, devices were no more or less likely to fail in either the control or intervention group, although the intervention group did receive more devices and were more likely to return their devices to the investigators. A possible explanation for the

higher intervention group device turnover is that they had access to their inhaler data and were therefore more likely to suspect malfunction, whether or not it was later shown. They were also less likely to be lost to follow-up with 83% of participants who were lost to follow-up coming from the control group.

Device failure rates in this study were higher than expected at 12% given our group's previous experience (163) but in line with the 12.5% median failure rate noted in the systematic review also presented in this thesis (see *Chapter 2*). In post-study testing, this figure was irrespective of batch, indicating systemic issues rather than batch-dependent problems. However, this still suggests 88% of devices returned by participants provided reliable data.

EMDs are a relatively new technology which are currently transitioning to use in the general healthcare market. Evidence supporting their value in improving adherence and asthma outcomes is mixed. Consequently, large scale, real world studies are still required to assess their value and place in routine clinical practice. This real-world study use of electronic monitoring devices highlights several issues. First, the pre-study and within-study failure rates, whilst not the highest seen in the literature *(see Table 4-1)*, have been disappointingly high

for newer generation EMDs. This suggests that there is still great value in conducting pre- and post-use quality control.

In this study, all 15 pre-study device failures were confirmed by the manufacturer and reported as being due to problems with the plastic casing. It is significant that these failures were not picked up by the manufacturer's own quality control system. Post-study failures appear to have been driven by the Fostair-compatible devices and it was noted over the same period that the manufacturer of the Fostair inhaler changed the structure of the Fostair inhaler itself. This is likely to have exacerbated any underlying device flaw. This also highlights a weakness in the current model where inhaler and EMD manufacturers are separate entities. Whilst this model allows for a unified platform across multiple inhalers, it reduces manufacturer agility in being able to adapt devices to changes in inhaler structure or develop devices to match new inhalers. The devices' reliability then depends on the relationships between the EMD manufacturers and their pharmaceutical colleagues.

On the EMD manufacturers' side, whilst the Smartinhaler™ system had been used widely in EMD studies previously, the newer generation models used in this particular study had only been validated in Pilcher et al.'s validation studies (165, 166) which demonstrated 75% rate of 100%-accurate SmartTurbo

devices and a 99.9% actuation detection rate for both the SmartTouch™ and SmartTurbo™ (see *Table 4-1*). To this author's knowledge, there are no published clinical trials using the SmartTouch™ and only two have used the SmartTurbo™, one of which did not report on device accuracy (157) and the other which reported no accuracy issues in devices which were not reported as broken, lost or forgotten or where there was no objective damage (69). This highlights an issue in terms of the validity of validation testing for previous models of a technology and the speed at which medical technologies can be evaluated. Newer models use Bluetooth upload capability for which bench testing data are only newly available. Our experience would suggest that more data are required. Validation testing is clearly required for every new model/generation brought to market at present; however, this will prove challenging if current processes for publishing validation data continue to be used. The technology appears to be developing more rapidly than studies are being published.

As recommended by Pilcher et al. (166), close communication with the manufacturer was essential in proceeding in this study. In this case, the manufacturer was extremely helpful in investigating and replacing potentially devices. It was noted that the manufacturer for EMDs used in this study was based in

New Zealand with demand for their product in the North American market. From discussions with the manufacturer, neither of these were large markets for Fostair, which was used extensively in our local clinics. It is therefore possible this lack of emergent need reduced the manufacturer's motivation to produce fixes for problems with the Fostair-compatible devices.

4.6.2. Study limitations

Whilst an *a priori* testing protocol was in place for pre-study testing, other testing procedures were developed as the study proceeded. In an ideal world, these would also have been developed *a priori* and their use in this pilot study would certainly inform protocol design were a larger study to be conducted.

The devices were checked by a single investigator who also conducted the study and issued devices, introducing a potential for unconscious bias and the risk of human error.

4.6.3. Implications for future use

Clinical studies

Our experiences underline the continued importance of quality control ('monitoring the monitors') in ensuring device validity. Other than the issues raised with Fostair-compatible plastic casings, device hardware was found to be consistently reliable.

However, without pre-study testing to exclude most unreliable devices, this may not have been the case.

Investigators should be aware of commercial considerations when planning real world studies. Manufacturer relationships with pharmaceutical companies, ability to respond to changes in the market and motivation to supply in a way that meets local practices will need to be discussed. Adherence studies are challenging to control for. This process is made more challenging when participants are asked to change their usual inhaler device as part of the clinical study. Manufacturers should be made aware of this prior to a clinical study being conducted.

Both issues highlight the importance of maintaining a good relationship with device manufacturers and raising issues arising in the study with them in real-time. Such relationships allow manufacturers to update designs and manufacturing procedures in a timely fashion, improving Research and Development in the EMD arena for future use.

The use of previously published protocols also allows for greater comparison and should be encouraged. Resources will need to be allocated to planning, designing and carrying out quality control procedures as well as liaising with manufacturers where issues do arise.

Generally, the number of devices which fail (i.e. miss actuation events) are cumulatively more than the number of events missed as the literature suggests. Missed events should be expected to be spread across a number of devices. Investigators should therefore report the proportion of failing devices with the same weight as the accuracy of recorded actuations when considering EMD reliability.

Clinical use

Unfortunately, whilst bench validation studies are encouraging, our experience highlights the fact that EMD testing using validated methodology remains essential. This has implications in the clinical setting, where data collected may be used to inform treatment decisions and where missed actuations may be mistaken for non-compliance. Burdening clinicians with quality control processes in a field of ever-changing technology is not sustainable. Furthermore, as will be seen in the reporting of the pilot study, the main selling-point of devices, and indeed part of their mechanism of action in increasing adherence, is reliant on the trust of the user that it accurately and objectively assesses their device use. This leaves little margin for error.

4.7. Conclusion

As part of a real-world study, 130 devices were tested prior to issue and 76 devices were tested after being returned. In both pre- and post-study testing, 12% of devices failed. This suggests that there remains a need for investigator quality control and close collaboration between investigators and manufacturers. Investigators should be aware that commercial factors and technological advancement may impact on individual model reliability. Stakeholders and manufacturers working in partnership should identify and address these problems such that, should definitive evidence of clinical benefit for EMDs in asthma become available, their real-world uptake is not delayed by a requirement for extensive quality control at the point of use.

Chapter 5: Improving asthma treatment using inhaler technology

5.1. Introduction

This thesis has previously discussed the fact that inhaled corticosteroid (ICS) underuse has been linked with poor outcomes in asthma, including exacerbation, hospitalisation and death (30-32, 150, 151). The UK based National Review of Asthma Deaths in 2014 highlighted the importance of poor adherence as a contributor to asthma mortality (12). Guidelines for asthma highlight the importance of adherence assessment in clinical practice (1, 6, 21), and stakeholders and researchers alike highlight adherence interventions as a research priority (5, 15, 152). In this chapter, a pilot study is presented which assesses the effect of an EMD-based adherence intervention on adherence and asthma control. This study hypothesised that access to feedback would improve both adherence and clinical decision-making and thus improve clinical outcomes, particularly severe exacerbations.

In *Chapter 3*, this thesis presented data suggesting that electronic monitoring device (EMD) based interventions improve adherence in asthma but have a less clear effect on clinical outcomes, particularly in adults (170). In that

discussion, the importance elucidating which components of EMD interventions mediated response and of considering pragmatic, real-world study design was highlighted. This pilot study isolated feedback from an investigator and mobile application (app) as its intervention to be clear on the intervention being tested so that intervention effectiveness could be properly evaluated. It was designed to minimise investigator input in order to be as close as possible to how EMDs could be integrated into future clinical care, with participants using, for the most part, their usual prescribed inhalers and treatment decisions being left in the hands of participants' usual clinical teams rather than investigator-driven.

The review noted a range of study populations, including those with over half of participants who had not required systemic steroids or admission for exacerbation in the preceding year. This is despite the evidence that previous exacerbation is a powerful risk factor for future exacerbation and the evidence that good ICS adherence is important in reducing exacerbation rate. This pilot study was therefore designed to enrich for exacerbation.

Also highlighted by the review of interventional studies was the importance of using outcome measures which were comparable

to other studies and clinically useful such as severe exacerbations, forced expiratory volume in one second (FEV_1) and standardised measures of symptom control such as the Asthma Control Test™ (ACT™) (170).

5.2. Methods

5.2.1. Study protocol

The study protocol with a list of trial amendments is included in Appendix C.

5.2.2. Study design

This was a randomised controlled trial with a 1:1 allocation to intervention and control groups. Participants were recruited for six months and followed up on an approximately monthly basis.

5.2.3. Recruitment, research site and ethics

Recruitment opened December 2016 and extended to December 2018. Participants were recruited from primary and secondary care, the Nottingham Respiratory Research Database (NRRD) and by public advertisement. Primary care sites included General Practices in Nottinghamshire, Derbyshire and Lincolnshire. Secondary care recruitment was carried out at respiratory clinics at Nottingham University Hospitals (NUH) NHS Trust, respiratory wards at NUH as well as the Emergency Department (ED) at NUH. The NRRD was a list of individuals

who were interested in being contacted for the purpose of research participation and who had consented to basic demographic, treatment and phenotyping information being held for this purpose. Public advertisement was conducted through display of posters at NUH, the University of Nottingham and General Practices in the catchment area as well as through advertisement on the Nottingham Respiratory Research Unit (NRRU) Facebook page.

Prior to being approached, patient records were screened for eligibility by the research team (NRRD and secondary care) or by the patient's General Practitioner (primary care). Contact details for the research team were provided directly to those approached in person, by telephone or by letter and also displayed on posters and online advertisements. Individuals who were interested then went through more detailed eligibility screening and, if likely to be eligible, were invited for a formal visit.

The study was conducted at the NRRU, Nottingham, UK. Occasional visits were also conducted in patients' local primary care practices (part of the East Midlands Primary Care Research Network) by prior arrangement. Ethics approval was gained from the London Central Research Ethics Committee. The NRRD

existed under a separate ethics agreement from the East Midlands Research Ethics Committee.

5.2.4. Eligibility criteria

Participants were included if the following were demonstrated at enrolment:

- Age 18-65 inclusive
- Systemic corticosteroid use for worsening asthma (or an increase from baseline dose in patients on long-term oral corticosteroids) in the prior 12 months (patient reported)
- Doctor's diagnosis of asthma for at least 12 months
- On British Thoracic Society (BTS) step 2-5 treatment via an inhaler compatible with a study monitoring device
- Use of own internet-enabled, compatible mobile phone
- Willingness and ability to give informed consent for participation in the clinical investigation
- Willingness and ability to comply with all clinical investigation requirements
- Willingness to allow their General Practitioner (GP) and consultant, if appropriate, to be notified of participation in the clinical investigation.

Participants were excluded if the following were demonstrated at enrolment:

- Diagnosis of chronic obstructive pulmonary disease (COPD) or onset of symptoms after the age of 40 in patients with ≥ 10 pack year history of smoking
- Other clinically significant coexisting respiratory disease e.g. fibrosis, bronchiectasis
- No personal mobile smartphone
- Use of maintenance and reliever therapy (MART)
- Any other significant disease or disorder which, in the opinion of the investigator, may have put the participant at risk, influenced the result of the clinical investigation or influenced the participant's ability to participate in the clinical investigation.

Use of a MART regime was excluded due to the complexity of analysing adherence and comparing it to standard regimens, particularly in the presence of potential ICS overuse patterns unique to MART and the exclusion/reduced reliance on SABA.

5.2.5. Randomisation

If screening was successful, participants were randomised to the intervention (EMD with app and investigator feedback) or control group (EMD, no feedback) using a 1:1 group allocation without stratification. To do this, the investigator conducting the baseline visit fed the participant's study identification number and date of birth into a database front-end. Permuted block

randomisation with a block size of six was then performed by a computer-generated algorithm, using the online tool from www.sealedenvelope.com (London, UK Copyright © 2001–2021 Sealed Envelope Ltd). The resulting allocation was displayed on the database front-end. The investigator then noted both the randomisation code and the group allocation and proceeded with the remainder of the baseline visit.

Given the nature of the study design, investigators were aware of group allocations. All participants were aware in vague terms that the EMD provided would look at patterns of inhaler use which would be reviewed by the end of the study and consented to participate in the study based on this. Once randomised, the study hypothesis and intervention procedures were discussed with participants in the intervention group, at which point they were asked to complete a second consent form. The existence of an intervention arm and the real-time capabilities of the EMDs were not discussed with control group participants until their final visit unless they requested this information directly.

5.2.6. Study procedures

General study procedures

These summarise the *Clinical Investigation Assessments*, the schedule of activities which can be found in *Appendix C* on *page 432*. At a baseline face-to-face visit conducted either at the

NRRU or at the patient's primary care practice, participants were screened and randomised (if they were found to be eligible on screening). They were then questioned on their asthma status and history (including exacerbations in the year preceding study entry). Spirometry, reversibility, asthma control (using the ACT™) and asthma-related quality of life (using the mini-Asthma Quality of Life Questionnaire [mini-AQLQ]) were measured. Participants were provided with a written asthma action plan and a Smartinhaler™ compatible with their inhaler. They also had their inhaler technique checked.

Participants were followed up for six months at approximately monthly intervals (giving a total of seven study visits). Follow-up visits were primarily over the telephone but were face to face if this coincided with routine hospital visits. All participants had their ACT™ and mini-AQLQ repeated monthly by an investigator. Participants were also asked to report any events, scheduled or unscheduled, that had taken place since their last study visit at this time. Usual care was provided by participants' own primary or secondary care team.

At a final visit conducted either at the NRRU or at the patient's primary care practice, participants again repeated the ACT™ and mini-AQLQ questionnaires, spirometry and reversibility and

reported any intervening events. All participants received feedback on their inhaler use data at this time. Finally, participants were invited to take part in a qualitative interview to discuss their experiences of being in the study and of using the EMDs provided. Findings from the interview are presented in *Chapter 6*.

Electronic monitoring device

The Adherium Smartinhaler™ platform was used to remotely record actuations, using Bluetooth® technology to periodically upload contemporaneous date and time stamps for actuations to the associated mobile app and from there to a cloud-based server (see also *Chapter 4*). Initially, devices were limited to SmartTouch™ devices which attached to compatible with Fostair, Salamol, Seretide and Ventolin MDIs as an external clip-on sleeve. SmartTurbo™ devices compatible with Bricanyl and Symbicort inhalers were also included later in the study. These clipped onto the base of the Turbohaler inhalers. Both the SmartTouch™ and SmartTurbo™ devices have been validated (165, 166) and were commercially available.

Depending on their study group allocation, participants were provided with either the Smartinhaler App™ (intervention group participants) or the Smartinhaler Lite App™ (control group participants). These are described in further detail below.

Intervention group additional procedures

In addition to the above procedures, intervention participants were also given feedback on their inhaler use data. This came from two sources. First, they were able to see their own data on a day-to-day basis in the app, which had a dashboard showing the proportion of expected inhaler actuations which had occurred that day. A further screen also showed a graph of actuations over a longer time period, with a line demarcating how many actuations were expected. In addition, the preceding month's data was reviewed by the investigator (IA). This was discussed with participants at Visits 2-6, with the emphasis of discussion on uncharacteristic SABA overuse or ICS underuse averaging <70%. Where there was evidence of SABA overuse or ICS underuse but not of device malfunction, these data were fed back to the participant's own clinical team and it was suggested to the participant that they discuss with their usual care team whether alterations to their management were required.

Control group

In order to maintain a level of partial blinding, control group participants saw a limited version of the mobile phone app which showed a cartoon of their device, the name of the inhaler it was linked to and the device's battery status as well as

whether or not it had been successfully paired. Data were not fed back to the usual care teams of control participants. At the final visit, the option to have a summary of their inhaler use data over the course of the study was provided with the option to relay this to their usual care teams themselves if they so desired.

Investigator roles

Three investigators (IA, NT, CP) conducted screening, randomisation and baseline study visits. Although not designated in the study protocol, NT conducted study visits 2-5 for control participants (with the exception of one visit – SIT006, Visit 3 conducted by IA) and IA conducted study visits 2-5 for intervention participants. NT did not access inhaler use data during the course of the study. All participants were seen at final visit by IA.

5.2.7. Clinical outcomes

Exacerbation events were defined as three or more days of systemic steroid use (or an increase in usual systemic steroid dose by at least double) in the context of acutely deteriorating symptoms of asthma. Events 14 or fewer days apart were counted as a single event.

The ACT™ is a questionnaire with response measured on a five-point scale. Good asthma control was considered to correspond to a score of 20 or more (171). The mini-AQLQ is a 15-item questionnaire split into four domains (symptoms, activities, emotions and environmental stimuli). To score, the mean of each domain was calculated in addition to the mean of all 15 questions. Each question was measured on a seven-point scale giving a maximum score of 7.0 for each of the domains as well as the overall test. Clinically meaningful improvement was considered to be 3 for the ACT™ (172) and 0.5 for the mini-AQLQ (173).

5.2.8. Study endpoints

Co-Primary endpoints

1. Preventer use: The mean percentage of prescribed ICS dose taken daily over the study period.
2. Reliever Use: The number of days with >16 actuations/day of short-acting beta agonist (SABA) taken in a 24-hour period.

For both primary and secondary adherence endpoints, each "day" has been defined as midnight to midnight.

Secondary endpoints: ICS use

1. Number of days of ICS non-use
2. Number of days of 100% preventer adherence

3. Mean percentage of prescribed preventer dose taken daily by month
4. Number of days of overuse of preventer treatment
5. Mean daily ICS (preventer) dose (total number of actuations over study period multiplied by dose per actuation) divided by number of days of treatment exposure

Secondary endpoints: SABA use

1. Overuse of reliever: Number of days of >24 and >32 actuations of SABA in a 24 hour period
2. Number of days of zero SABA use

Secondary endpoints: power calculation

Derivation of a power calculation for a real-world study, based on adherence

Secondary outcomes: clinical control

1. Number of exacerbations (treatment with systemic corticosteroids for asthma or antibiotics)
2. FEV_1
3. Asthma control (ACT™ score)
4. Asthma-related quality of life (Mini-AQLQ score)

Secondary outcomes: treatment decisions

1. Studying the utility of differing thresholds for feedback (e.g. ICS adherence of <75% or <80%; SABA thresholds based on number of days of at least one SABA actuation or maximal daily number of actuations)
2. Study practicality of data feedback processes

3. Episodes where advice provided to seek GP/clinical review based on monitoring data; and, episodes when participants actually sought review subsequently

* *assessed via interview at final visit*

5.2.9. Statistical plan

The study sample size was chosen in keeping with the study's nature as a pilot study. Quantitative data were analysed using STATA v15, StataCorp LLC (Texas). For the Intention to Treat (ITT) analysis, all participants who provided any data were included. Participants who provided no data were excluded as it could not be determined whether this non-provision of data was due to non-use or device fault. Participant data were included up to the last day of data provision.

Parametric continuous data were summarised using means and standard deviations (SD) and non-parametric data were summarised using medians and inter-quartile ranges (IQR). Daily ICS adherence has also been reported using means and SDs in line with the literature. A student's *t*-test was used to test for differences in adherence and parametric outcomes. Wilcoxon's Rank Sum statistic was used to test for differences in non-parametric continuous clinical outcomes. Chi-squared tests were used for categorical outcomes and a mixed-effects linear regression model was used to assess the effect of study group on ICS adherence over the course of the study. The

mixed effects model was chosen in order to account for the fact that this outcome involved monthly repeated measures from participants.

Secondary outcome SABA data was calculated as the number of participants with any recorded overuse at each threshold. SABA non-use was as the number of days of non-use per person-days, accounting for varying durations of study participation.

Exacerbation rate was analysed per 1000 person-days to account for differing durations of study participation. Exacerbations were also expressed categorically as participants who had experienced exacerbation *vs.* participants who had not using the chi-squared statistic.

To assess utility of differing thresholds of adherence, cut-offs were defined as follows:

- Preventer use recorded at 50%, 60%, 70%, 75%, 80% and 90% prescribed
- SABA use of ≥3 days per week (equivalent to poor control and suggestive of need for escalation of therapy) (1)
- SABA use equivalent to use more than one canister per month (i.e. >120 actuations of terbutaline and >200 actuations of salbutamol (6, 174, 175)).

These cut-offs were assessed by study group using the chi-squared statistic to ascertain whether there was a significant difference between groups. Selected cut-offs were then assessed against clinical outcomes using student's *t*-test for parametric data and Wilcoxon's Rank Sum for non-parametric data.

A major concern during the study was the role faulty devices may have played in study outcomes. To combat this, a sensitivity analysis was carried out using only trusted devices to assess whether elimination of faulty or potentially faulty devices would have any effect on outcomes. These were devices which were either returned for testing and passed post-study testing or were not returned by participants but had no major concerns during their study usage.

5.3. Results and analysis

5.3.1. Recruitment

In total, 36 participants were randomised, 18 to the intervention group and 18 to the control group (*see Figure 5-1*). Recruitment took place over a period of 24 months (*Figure 5-2*). Overall, 30 participants attended the final visit for the study. Four participants did so having missed intervening visits either due to difficulty contacting them to arrange these visits or, for one participant, due to a request to withdraw from the

study. Six participants were lost to follow-up. Five of these were control participants. Thus, 14 intervention and 12 control participants completed all study visits and 17 intervention and 13 control participants attended the final visit.

Data were obtained from 33 participants (18 intervention and 15 control participants). All 33 were included in the analysis. For one intervention participant, technical issues meant that their real-time data were not available to either them or to the investigators for monthly feedback. Their data were analysed according to group allocation regardless. Duration of ICS data analysed ranged from 35 days of data to the full 168 days.

Figure 5-1: CONSORT diagram of study recruitment

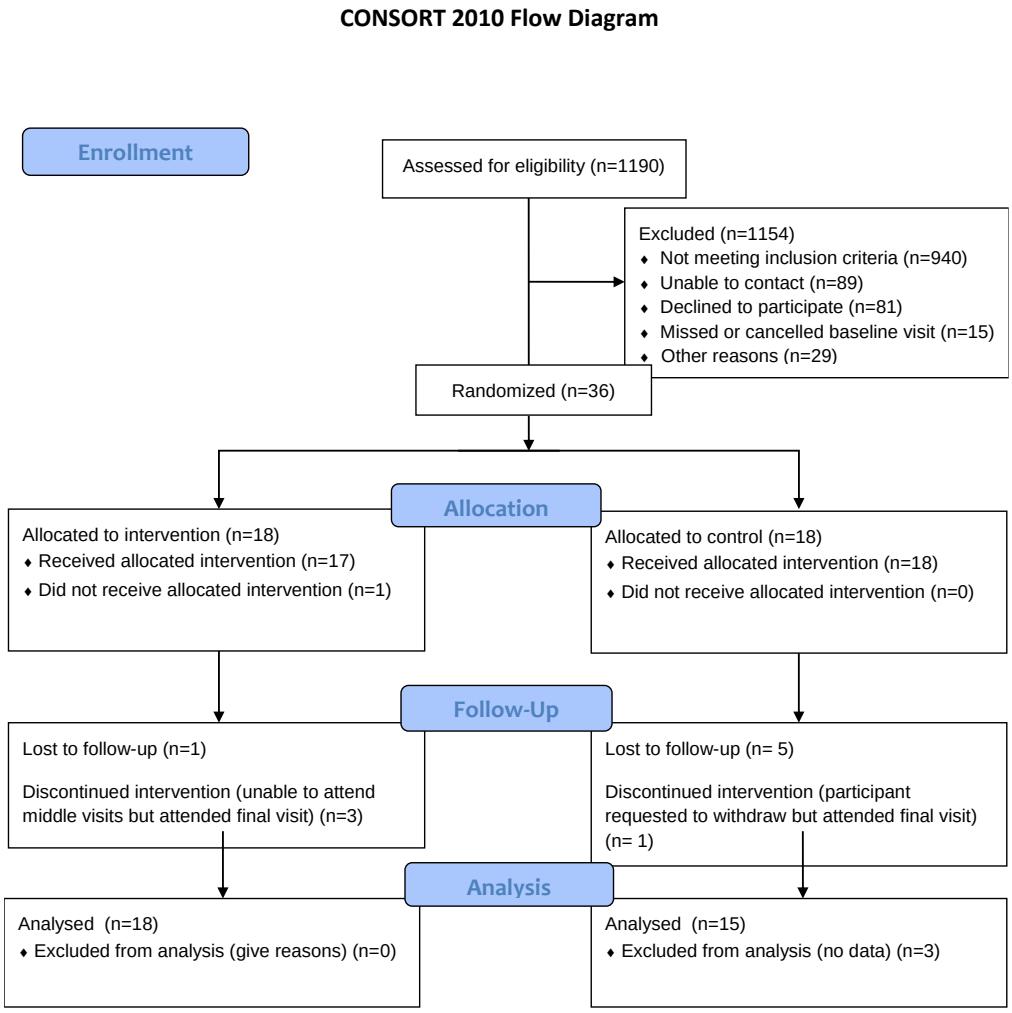
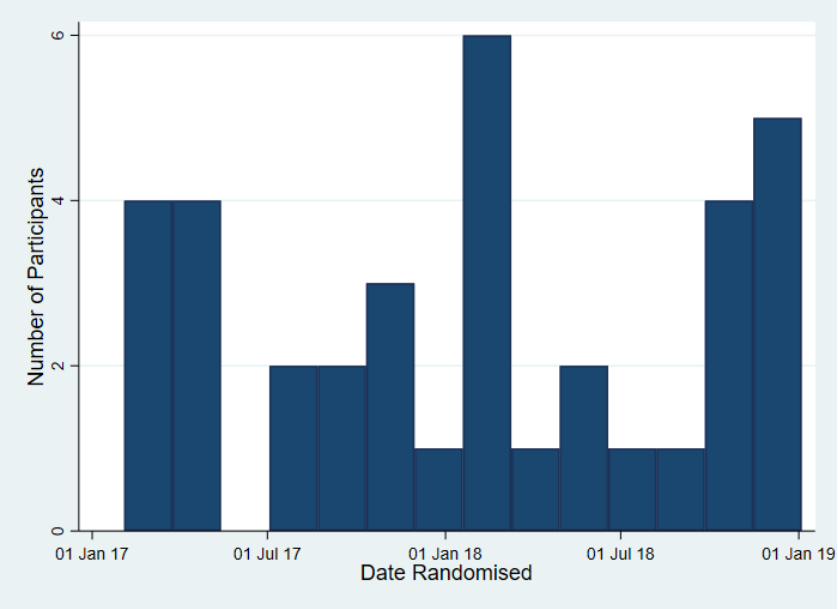


Figure 5-2: Recruitment over study period



5.3.2. Baseline characteristics

Baseline demographics are shown in *Table 5-1*. Participants' ages ranged from 18 to 64. Sixty-seven percent of participants were female and the majority of participants (83%) identified as Caucasian. Other than a slightly higher age at both enrolment and diagnosis in the intervention group, the intervention and control groups were relatively well-matched demographically. Participants who attended Visit 7 and the six participants who were lost to follow-up (and consequently had few or no days of data) were also well-matched (*Table 5-2*). In terms of baseline asthma severity and phenotype, half of the participants had evidence of inflammation (either an eosinophil count of >0.4 $x10^{-9}$/L or F_ENO of ≥40 ppb), just under half had evidence of atopy (total IgE of >100 kU/L or allergen-specific

IgE positive >0.35 kU/L) and two thirds were never smokers. These were evenly split between the groups.

Table 5-1: Baseline participant characteristics

	Overall (n=36)	**Intervention (n=18)**	**Control (n=18)**
Age, median (IQR)	48.3 (33.5, 55.4)	50.0 (34.9, 58.6)	43.5 (32.2, 50.9)
Female, n (%)	24 (67)	11 (61)	13 (72)
Caucasian race, n (%)	30 (83)	16 (89)	14 (78)
Years since diagnosis, median (IQR)	23.5 (12.5, 37.0)	23.0 (7.0, 35.0)	26.0 (14.0, 39.0)
Approximate age at diagnosis, median (IQR)	15.12 (4.9, 30.6)	17.0 (4.8, 45.0)	13.5 (4.9, 27.6)
BTS stage, n (%)			
3	8 (22)	4 (22)	4 (22)
4	22 (61)	10 (56)	12 (67)
5	6 (17)	4 (22)	2 (11)
ICS dose*, median (IQR)	1600 (800, 1600)	1600 (800, 1600)	1600 (800, 1600)
Evidence of inflammation, n (%)	18 (50)	9 (50)	9 (50)
Evidence of atopy, n (%)	17 (47)	9 (53)	8 (47)
History of reversibility, n (%)	6 (16.67)	2 (11)	4 (22)
Smoking status, n (%)			
Smoker	3 (8)	2 (11)	1 (6)
Ex-smoker	9 (25)	4 (22)	5 (28)
Never smoker	24 (67)	11 (61)	13 (67)
Pack years, median (IQR)	8.25 (4.18, 13.50)	8.25 (6.00, 9.50)	8.84 (2.59, 22.50)
BMI, mean (SD)	30.75 (7.23)	32.04 (8.66)	29.37 (5.24)

** Beclometasone diproprionate equivalent (BDPe), micrograms*

Table 5-2: Demographics by loss to follow-up

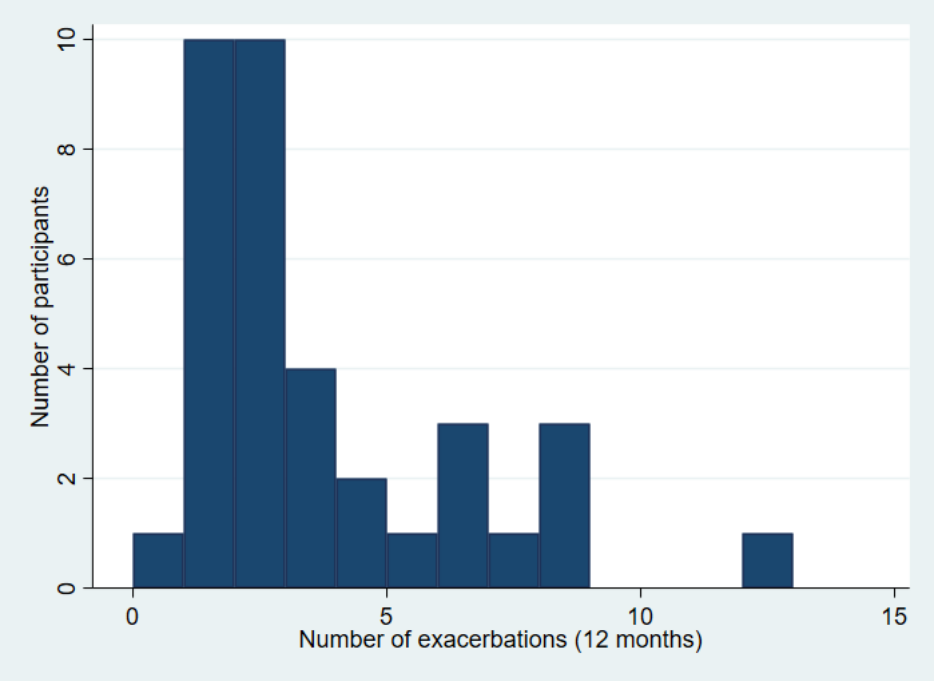
	Attended V7 (n=30)	**Lost to follow-up (n=6)**	*p*
Age, median (IQR)	46.7 (34.9, 54.3)	50.4 (26.1, 56.4)	0.932
Female, n (%)	19 (63)	5 (83)	0.900
Caucasian race, n (%)	25 (83)	5 (83)	1.000

There was a difference between the groups in baseline mini-AQLQ (*Table 5-3*). The intervention group also had a slightly higher proportion of participants with uncontrolled asthma as measured by the ACT™ and a slightly lower median percentage predicted FEV_1. The groups had a similar exacerbation profile. Self-reported exacerbations were confirmed for all but one participant (*Figure 5-3*).

Table 5-3: Baseline participant asthma control

	Overall (n=35)	**Intervention (n=18)**	**Control (n=17)**
Pre-bronchodilator FEV_1 (L), median (IQR)	2.47 (1.50, 3.06)	2.39 (1.55, 2.86)	2.47 (1.50, 3.06)
FEV_1 percent predicted, median (IQR)	75.5 (48.6, 90.4)	73.8 (54.5, 86.5)	82.2 (48.6, 95.9)
FEV_1 reversibility (%), median (IQR)	4.13 (1.25, 13.14)	7.99 (1.50, 13.14)	3.47 (1.21, 7.09)
Proportion reversible at baseline, n (%)	12 (33.33)	6 (33)	6 (33)
	Overall (n=36)	**Intervention (n=18)**	**Control (n=18)**
ACT™ score, mean (SD)	14.9 (4.9)	13.6 (4.5)	16.3 (4.9)
Uncontrolled by ACT™, n (%)	30 (83)	17 (94)	13 (72)
AQLQ score, median (IQR)	4.97 (3.73, 5.97)	4.33 (3.40, 5.47)	5.47 (4.60, 6.13)
Exacerbations in preceding 12 months, median (IQR)	2 (1, 5)	2 (1, 6)	2 (1, 4)
Participants with ≥3 exacerbations in preceding 12 months, n (%)	15 (42)	8 (45)	7 (39)
Hospitalisation ever, n (%)	26 (72)	14 (78)	12 (67)
Critical care ever, n (%)	10 (28)	5 (28)	5 (28)

Figure 5-3: Number of confirmed exacerbations in year preceding enrolment



5.3.3. Co-primary endpoints

Table 5-4 presents the data for the co-primary endpoints. Three participants were excluded from the intention to treat analysis as they were lost to follow-up after their first visits and had no data upload from their devices. Three further participants were lost to follow-up and four did not complete all study visits. Data for these seven were analysed for the duration over which they provided data. There was no significant difference between intervention and control group adherence or SABA overuse

(>16 puffs per day) over the study period. This did not change on sensitivity analysis *(Table 5-5)*.

Table 5-4: Mean daily preventer adherence and bronchodilator overuse by study group

	Overall, n=33 (%)	**Intervention, n=18 (%)**	**Control, n=15 (%)**	*p*
Percentage mean daily ICS adherence, median (IQR)	80.8 (36.6, 92.4)	84.6 (43.6, 96.5)	53.4 (36.3, 88.2)	0.366
Mean percentage daily ICS adherence, mean (sd)	65.6 (32.0)	70.7 (32.1)	59.4 (31.9)	0.319
Median days > 16 SABA puffs (IQR)	0 (0, 0)	0 (0, 2)	0 (0, 0)	0.648

Table 5-5: Mean daily preventer adherence and bronchodilator overuse by study group: Sensitivity analysis (trusted devices)

	Overall, n=23 (%)	**Intervention, n=13 (%)**	**Control, n=10 (%)**	*p*
Percentage mean daily ICS adherence, median (IQR)	85.8 (43.6, 92.4)	85.9 (53.3, 96.3)	67.1 (33.3, 88.2)	0.352
Mean percentage daily ICS adherence, mean (SD)	68.9 (31.1)	74.4 (28.2)	61.7 (34.8)	0.343
	Overall, n=26 (%)	**Intervention, n=14 (%)**	**Control, n=12 (%)**	*p*
Median days > 16 SABA puffs (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0.754

5.3.4. Secondary endpoints

ICS use

There were no significant differences between intervention and control groups for the rate days of ICS non-use, 100% ICS adherence, ICS overuse, mean daily ICS dose by month and mean daily ICS dose overall *(Table 5-6)*.

Table 5-6: Secondary endpoints - preventer use

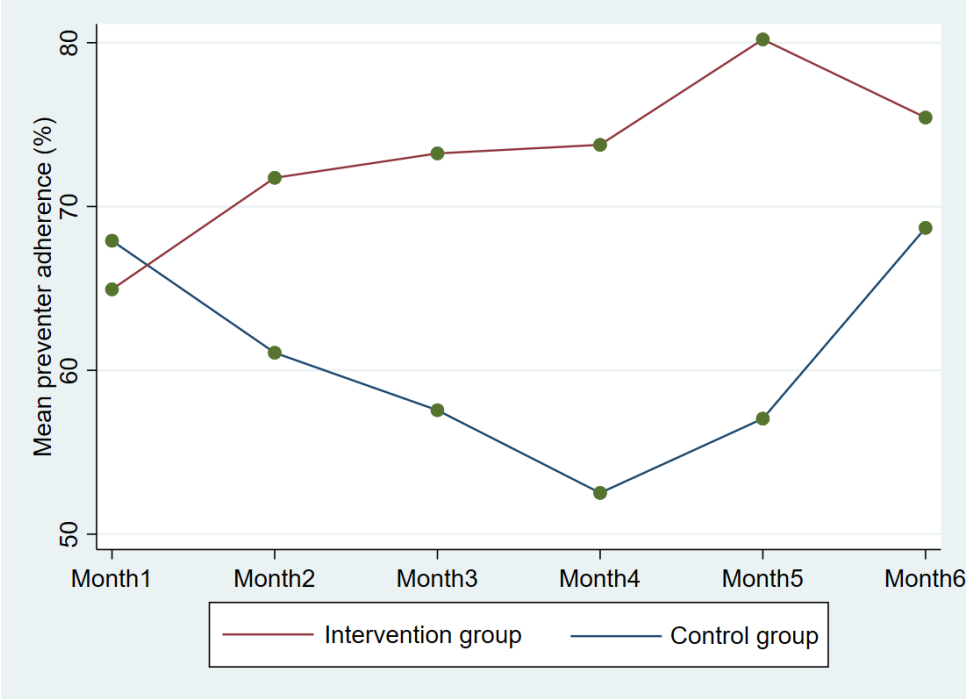
	Overall, n=33 (%)	**Intervention, n=18 (%)**	**Control, n=15 (%)**	*p*
Preventer non-use*, median (IQR)	0.06 (0.01, 0.35)	0.04 (0.01, 0.35)	0.08 (0.02, 0.38)	0.503
100% preventer adherence*, median (IQR)	0.35 (0.07, 0.67)	0.45 (0.10, 0.68)	0.26 (0.04, 0.61)	0.148
Preventer overuse*, median (IQR)	0.05 (0.03, 0.08)	0.06 (0.03, 0.11)	0.05 (0.01, 0.07)	0.470
Mean daily ICS dose per day exposed†, median (IQR)	772 (390, 1450)	731 (390, 1550)	949 (353, 1398)	0.691

** Per person-days*
† BDPe, micrograms

A repeated measures mixed effects model to assess difference in adherence between groups on a month by month basis was not significant for time (coefficient -0.1%, 95% CI -1.5 to 1.3, p=0.849) or study group (coefficient 11.5%, 95% CI -9.7 to 32.7, p=0.287). However, whilst there was no overall difference, a linear plot of adherence by month suggested a

separation between the groups in the middle part of the study which resolved in the final month when control participant adherence drastically increased *(Figure 5-4)*.

Figure 5-4: Mean preventer adherence by month



Reliever use

The rate per person-days where SABA was not required is presented in *Table 5-7*. Three thresholds for reliever overuse were considered: >16 SABA actuations in one day, >24 SABA actuations in one day and >32 SABA actuations in one day. For each of these thresholds, the number of participants who **did not** demonstrate SABA overuse at any point in the study are presented. There were no statistical differences in reliever use between intervention and control groups for either the rate days of non-use or the rate of overuse days of SABA.

Table 5-7: Secondary endpoints - reliever use

	Overall, n=33 (%)	**Intervention, n=18 (%)**	**Control, n=15 (%)**	*p*
Reliever non-use*, median (IQR)	0.81 (0.43, 0.92)	0.71 (0.46, 0.83)	0.83 (0.27, 0.96)	0.448
Overuse >16 reliever actuations/24h†, *n* (%)	8 (24)	5 (28)	3 (20)	0.604
Overuse >24 reliever actuations/24h†, *n* (%)	6 (18)	4 (22)	2 (13)	0.510
Overuse >32 reliever actuations/24h†, *n* (%)	2 (6)	0 (0)	2 (13)	0.110

** Per person-day*
† Number of participants with one or more episodes of overuse as described

Power calculation

A power calculation to predict sample size needed to detect a difference in ICS adherence between groups based on this study design of feedback *vs.* no feedback was derived using levels of ICS adherence from this study. Power was set at 90% to account for loss to follow-up. For a difference in daily ICS adherence of 11% between the intervention and control groups and significance level of 0.05, a sample of 340 (170 per group) would be required.

Clinical control

Exacerbations, defined as usually seen in the literature (176, 177) as acute deterioration of symptoms and three or more days of systemic steroids or doubling of usual steroids, are presented below *(Table 5-8)*. Also presented are exacerbations where this definition is expanded to include antibiotics. When defined as symptoms and steroid or antibiotic use, there was a borderline significant higher exacerbation rate in the intervention group. There was no correlation between exacerbation rate and adherence. Pearson's *r* statistic was -0.06 (p=0.731) for exacerbations measured by steroid use only and -0.15 (p=0.402) for exacerbations measured by steroid and antibiotic use. A box-plot below shows median adherence grouped by number of exacerbations over the study period *(Figure 5-5)*.

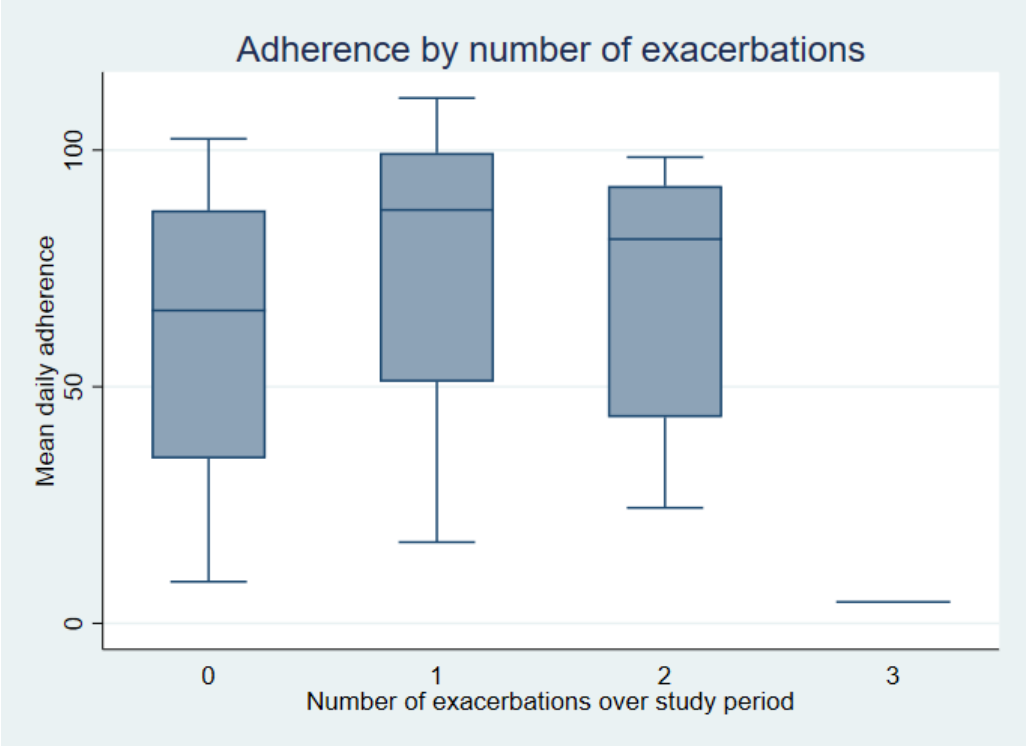
Whilst there were no other significant findings in clinical outcomes, it should be noted that the significant difference in asthma-related quality of life and the trend towards a difference between groups in asthma control seen at baseline was no longer present at the end of the study, suggesting a possible trend towards a greater change in asthma-related quality of life and asthma control in the intervention group.

Table 5-8: Secondary outcomes - clinical control at final visit

	Overall (n=36)	**Intervention (n=18)**	**Control (n=18)**	*P*
Total exacerbations *	24	16	8	0.276
Total exacerbations † **(including antibiotics)**	27	19	8	0.055
Exacerbation rate‡* **(95% CI)**	1.66 (1.11, 2.48)	1.99 (1.21, 3.24)	1.25 (0.63, 2.51)	0.245
Exacerbation rate‡† **(including antibiotics, 95% CI)**	1.87 (1.28, 2.73)	2.36 (1.51, 3.70)	1.25 (0.63, 2.51)	0.069
Percentage predicted FEV_1, median (IQR)	79.4 (51.3, 89.6) ***n=29***	72.9 (59.7, 79.3) ***n=17***	82.0 (48.3, 90.5) ***n=12***	0.626
ACT™, mean (sd)	16.6 (5.84) ***n=30***	15.5 (5.84) ***n=17***	18.1 (5.84) ***n=13***	0.232
Mini-AQLQ, median (IQR)	5.3 (5.1, 6.7) ***n=30***	5.3 (3.9, 6.3) ***n=17***	5.3 (5.1, 6.7) ***n=13***	0.295

** Asthma symptoms and systemic steroids*
† Asthma symptoms and systemic steroids or antibiotics
‡ Per person-year

Figure 5-5: Adherence by number of exacerbations



p=0.397

Treatment decisions

Feedback thresholds

The table below demonstrates that the intervention group had more adherent participants than the control group. This was borderline significant at an adherence threshold set at 75-80% *(Table 5-9)*. Clinically, however, this does not appear to translate into a difference in outcomes *(Table 5-10)*.

Table 5-9: Proportion of participants with good adherence by study group

Adherence threshold	Intervention group (n=18) – proportion good adherence, *n* (%)	Control group (n=15) – proportion good adherence, *n* (%)	p
50%	13 (72)	9 (60)	0.458
60%	12 (67)	6 (40)	0.126
70%	12 (67)	6 (40)	0.126
75%	12 (67)	5 (33)	0.056
80%	12 (67)	5 (33)	0.056
90%	7 (39)	3 (20)	0.240

Table 5-10: Clinical outcomes at final visit compared between participants with good adherence and poor adherence (defined at a 75% threshold)

Outcome	Participants with ≥75% adherence (n=16)	Participants with <75% adherence (n=14)	p
Percentage predicted FEV_1, median (IQR)	67.6 (45.2, 84.6) ***n=15***	87.9 (62.8, 91.4)	0.206
ACT™, mean (SD)	17.4 (5.8)	15.6 (6.0)	0.411
mini-AQLQ, median (IQR)	5.43 (4.13, 6.50)	5.23 (4.60, 6.33)	0.868
Participants experiencing ≥1 exacerbation*, *n* (%)	10 (59%) ***n=17***	7 (44%) ***n=16***	0.387

**Asthma symptoms and systemic steroids*

In total, 753 weeks of reliever data were examined for use on three or more days of the week. Overuse by this threshold was observed on 294 weeks (39% weeks). Overall, 188 months were examined for reliever use equivalent to a whole canister in a single month. Overuse by this threshold was observed on 15 months (8% months). There were no differences between

the groups in the number of participants who did not overuse their reliever inhaler *(Table 5-11)*.

Table 5-11: Proportion of participants with no inappropriate SABA use by study group

Adherence threshold	Intervention group (n=18) – no inappropriate use, *n* (%)	Control group (n=15) – no inappropriate use, *n* (%)	p
Poor control (≥3 days per week)	3 (17)	4 (27)	0.484
Overuse (≥1 canister per month)	15 (83)	14 (93)	0.381

In terms of clinical outcomes, participants with an overuse pattern suggestive of poor control demonstrated clinically and statistically significant lower asthma control and asthma-related quality of life than participants not demonstrating this pattern of reliever overuse *(Table 5-12).* Similarly, participants who had used the equivalent of a full canister of reliever inhaler in any one month demonstrated a lower percentage predicted FEV_1, lower asthma control score and were more likely to have experienced at least one exacerbation (defined as symptoms and systemic steroid use) at the study end (*Table 5-13*).

Table 5-12: Clinical outcomes at final visit compared between participants with appropriate SABA use and SABA use on ≥3 days per week

Outcome	Appropriate use (n=6)	Use on ≥3 days per week (n=24)	p
Percentage predicted FEV_1 median (IQR)	83.5 (67.6, 89.6)	77.2 (45.2, 91.4) ***n=23***	0.554
ACT™, mean (SD)	22.7 (2.9)	15.1 (5.3)	**0.003***
mini-AQLQ, median (IQR)	6.77 (6.60, 6.87)	5.20 (4.03, 5.93)	**0.001***
Participants experiencing ≥1 exacerbation, *n* (%)	2 (29) ***n=7***	15 (58) ***n=26***	0.171

Table 5-13: Clinical outcomes at final visit compared between participants with appropriate SABA use and SABA overuse equivalent to a whole canister in any month

Outcome	Appropriate use (n=26)	Overuse (n=4)	p
Percentage predicted FEV_1, median (IQR)	83.7 (62.8, 91.4) ***n=25***	42.1 (35.7, 56.7)	**0.019***
ACT™, mean (SD)	17.5 (5.6)	11.0 (5.0)	**0.037***
mini-AQLQ, median (IQR)	5.60 (4.60, 6.60)	4.40 (2.83, 5.43)	0.127
Participants experiencing ≥1 exacerbation, *n* (%)	13 (45) ***n=29***	4 (100) ***n=4***	**0.038***

Feedback practicality

Five intervention participants were referred to their GP for six occasions of ICS underuse (<70%) and 10 intervention participants for 22 occasions of SABA overuse (more than usual for them). There are 10 occasions where asthma reviews in primary care appear to coincide with these referrals suggesting an uptake rate of 37-45%.

In practice, feedback was complicated by concerns about device reliability, individual need (some participants, for example, reported that because they were already on maximal treatment, feedback of SABA use to GPs did not result in treatment changes as there was no further escalation possible in primary care) and place of care. Where care for a patient was coordinated by tertiary care, the provision of data to severe asthma teams served more as information – participants did not report specific actions resulting. Finally, where participant visits were delayed, this resulted in a delay in feedback as verbal consent was taken at these visits to share information.

5.4. Discussion

Study findings

A real-world randomised controlled pilot study was designed to investigate the effect of providing in-app and investigator feedback on EMD-measured inhaler adherence. Whilst an 11% difference between intervention and control arm ICS adherence was observed, this was not statistically significant and a power calculation suggests that the study is significantly underpowered to find a difference in adherence using this design. This study also found a non-significant difference in exacerbation rates in favour of the control arm. With a broader definition for exacerbations, this difference in exacerbation rate

approached statistical significance. There were no statistically significant differences in clinical outcomes between the groups.

When assessing treatment decisions, a greater proportion of the intervention group had an adherence level of ≥75% compared with the control group, although this had only borderline significance (p=0.056) and was not associated with a difference in clinical outcomes. There was no difference in SABA overuse between the groups; however participants who overused their SABA demonstrated a lower percentage predicted FEV_1, asthma control and asthma-related quality of life score as well as a higher exacerbation rate at their final visit.

Also of interest was the increase in adherence in the control group ahead of their final study visit, suggesting that, although many control participants expressed awareness that they were being monitored *(see Chapter 6)*, this did not lead to maintained adherence throughout the study period. In keeping with this finding, more participants in the control group were also lost to follow-up.

Current evidence and context: study design

EMD-measured inhaler adherence has become increasingly accurate, with newer devices including capabilities such as detection of inhalation and inhaler technique (5, 178, 179). In

Chapter 3, this thesis presents evidence that EMD research strongly supports the role of EMD-based interventions in improving ICS adherence; however, previous studies have not always been clear on which component of an intervention has led to its effect. Surprisingly, it also suggests that, despite the strong link between poor adherence and outcomes in asthma, there remains little evidence, particularly in adults, that EMD based interventions lead to improved outcomes in asthma. Potential reasons for this include recruitment of participants with high baseline adherence or at lower risk of adverse outcomes, such that a change would not be observed in the three to twelve month study periods commonly employed in adherence studies. Importantly, no study has thus far been able to define the magnitude of change in adherence needed to lead to a change in clinical outcomes.

We designed a pilot study that would be as close to real world in nature as possible. Our protocol enriched for individuals with asthma who were at risk of exacerbation and narrowed the observed EMD-based intervention to clinician and app feedback. Despite this, our study did not observe a statistically significant change in mean daily ICS adherence, nor did it observe a statistically significant difference in SABA overuse. The study did demonstrate a non-significant difference in adherence

(compared with most studies which have found significant between-group difference). This lack of significance in the context of previous evidence suggests that clinician/app feedback may act synergistically with other elements of EMD-based intervention (such as reminder alarms), but may be less effective when used alone. This is supported by the power calculation which indicates that, as a solitary intervention, a sample of 340 participants would be needed to see a significant difference in adherence between the intervention and control groups.

The non-significant adherence rate difference between the groups of 11% is in keeping with the estimate from the meta-analysis in *Chapter 2*, which suggests that interventions may expect to see a roughly 13% improvement in adherence. In *Chapter 3*, however, this thesis discussed that, given the high baseline adherence of interventional study participants, such increments in adherence may be too small to translate into improved clinical outcomes. Furthermore, the studies in *Chapter 3* which did show a translation of adherence improvements into clinical outcomes had effect sizes of around 20% and 50% (69, 71). Whilst, as per the original investigation plan, the effect size for the power calculation was drawn from the results of this study, the possibility that a much larger effect

size may be required to see a translation from improved adherence to improved clinical outcomes should be considered.

More complex adherence outcome measures (inhaler technique outputs for example, or accounting for the effect of seasonal changes) may be informative but there is currently little in the literature to support their use as primary outcomes. Future studies should certainly consider these important factors and incorporate such outputs into the analysis plan where appropriate.

Current evidence and context: clinical outcomes

Evidence suggests that increased adherence leads to reduction in exacerbation rates (31, 32, 180); however, in this study, the opposite was noted. Whilst this study was pilot in nature and not powered for exacerbations, it does suggest that in a real-world setting where changes in care are provided by an individual's usual care team, factors other than adherence may influence clinical outcomes. This may shed some light on why, despite positive effects on adherence, EMD-based interventions have not led to the improvements in clinical outcomes expected.

Potential candidate factors have emerged from interviews with participants *(see Chapter 6 – Results: Participants' experiences of the Inhaler Technology Study)* who consistently reported that

the main impact of study participation was on their awareness of their condition and medication use. It may be that, for intervention participants, the combination of this awareness with app and/or investigator feedback led to the increased frequency of exacerbation observed. Another possibility is that the process of GP referral as an intervention may have led to an increase in help-seeking behaviours not seen in the control group. Lastly the real-time in-app access may have played into health anxieties which emphasised symptoms that would previously have been ignored.

Whilst these factors may modify the risk of exacerbation in EMD-based interventions, they may also maintain engagement. More participants from the control group (who did not receive regular feedback) were lost to follow-up. It may be that the regular feedback led to increased engagement with a proportion of device users who may not otherwise have remained engaged.

These findings have implications for future real-world studies in asthma where responsibility for clinical management is placed with the usual care team and exacerbations are defined based on symptoms. Increased symptom awareness or even engagement should not be presumed to be beneficial and the potential effects of increased help-seeking and/or anxiety should be mitigated for.

SABA overuse did not differ between the groups, however it did appear to be associated with clinical outcomes. This was demonstrated with thresholds from both the Global Initiative for Asthma (≥3 days of use in a given week) and the BTS (more than one canister in a given month) (1, 6). Patel et al. have previously demonstrated that electronically-monitored SABA overuse may identify individuals at risk of poor asthma control (96) and hospitalisation (95). Whilst use of more than one canister a month would be flagged on electronic records, the softer overuse definition of ≥3 days of use a week would not necessarily, suggesting a possible role for EMDs in identifying moderate SABA overuse.

Even where such a role is found, however, there remains a question of standardising an appropriate response. No participants whose care was primarily under tertiary services reported any change as a result of data being sent to their healthcare team. This is likely to be because there was no clear pathway for action and participants under tertiary care were generally on maximal treatment already. Thus, future interventions would need to be tailored to individual users' needs and have a clear process of response.

Study limitations

This study was limited by lower levels of recruitment than planned and a high attrition rate (17%), particularly in control participants. Note is made of the significant shift towards MART regimes, which are now enshrined in guidelines (6, 24). This study excluded individuals using a MART regime and findings cannot be generalised to this group. Given the marked rise in the usage of MART regimes and their inherent potential for increased ICS exposure, a future study must consider how to incorporate them into its analysis. The study was also hampered at various points by poor device performance, and post-study testing revealed a small subset of devices with potentially unreliable results, although this has been accounted for in the sensitivity analysis. Due to its nature as a pilot study, one investigator performed both interim analysis of adherence data and outcome monitoring, which could have been a source of observer bias.

As a pilot study, a study goal was to calculate the sample size that would be needed to adequately power this study design. Due to the fact that the study has been found to be significantly underpowered, caution is exercised in generalising its findings.

Strengths of the study include its nature as a randomised controlled study and its real-world nature which increases its

applicability to clinical practice. Participants were not excluded on the basis of multi-morbidity or smoking unless the smoking history increased the likelihood of chronic obstructive pulmonary disease, again increasing its applicability. The mixture of participants from primary and tertiary care allows for implications to be drawn for both populations. Finally, clinically useful and validated outcome measures were collected, allowing for a level of comparability to both existing evidence and clinical practice.

Learning from this study

Future studies of EMD-based interventions should aim to use feedback to maintain adherence in combination with one or more other elements of EMD-based intervention (such as reminder alarms). From a clinical control perspective, further research into both the threshold of adherence and the magnitude of change in adherence required to bring about improvement in clinical outcomes is still required. There may be a role for electronic SABA monitoring to identify individuals with moderate overuse at risk of poor asthma control. Having said this, despite their popularity with study participants, EMD-based interventions may not have as direct a relationship with clinical outcomes as previously thought. Further research is

therefore recommended before their routine adoption in clinical practice.

5.4.1. Conclusion

A pilot study of an EMD-based adherence intervention suggests that feedback alone does not lead to a significant improvement in adherence. Further work on the threshold and magnitude of adherence required to see an improvement in clinical outcomes is needed. Elucidation of the mechanisms by which adherence interventions influence clinical outcomes is required, particularly as they may not be as direct as previously thought. This should happen before EMD-based interventions are introduced into routine clinical practice.

Chapter 6: Experience of Smartinhaler™ technology – patient perspectives

6.1. Introduction

A qualitative study was conducted as part of a pilot study of adherence (see *Chapter 5*). This was done to gain a deeper understanding of how study participants viewed their asthma, its treatment, their participation in the study (with particular focus on their experience of using electronic monitoring devices [EMDs]) and the acceptability of potential future avenues of EMD use. By considering aspects which fall outside the focus of quantitative inquiry, a qualitative approach opens up the opportunity to engage individuals with asthma in their own care.

This chapter examines the theoretical underpinnings for qualitative inquiry and discusses the reasons behind the methodology chosen for the study. Study findings will then be presented and, by situating findings from this specific cohort in the context of current evidence, potential implications for future EMD use will be suggested.

6.1.1. Current evidence in the use of EMD interventions for behaviour change

Whilst there has been extensive quantitative research into the measurement of adherence and interventions for poor adherence in asthma (35, 45, 46, 103) and a growing and significant body of work into barriers to adherence in asthma (43, 54, 56, 59, 62, 83, 181-183), as well as enquiries into user acceptability (71, 168), there has been little work done directly aimed at understanding individual experiences of EMDs with relation to inhaled corticosteroid (ICS) adherence (152).

Two adolescent and one adult study have been identified which used in-depth semi-structured interviews to achieve a similar aim to that described above (184-186). Howard et al. (185) looked at attitudes of adolescents with asthma towards an earlier iteration of the Smartinhaler™ through the medium of structured interviews. Seven adolescents used the devices for a one month period. In this observational study, investigators found that adolescents felt more positively towards it than towards other forms of adherence monitoring. Adolescents reported feeling that it gave them an increased sense of control over their condition as well as increasing their sense of responsibility and making it clear to others that they were responsible. They felt that the awareness that their parents and

clinicians were potentially monitoring their inhaler use may have affected their inhaler use behaviours and discussed how it helped them talk about their asthma status with their healthcare team. They were aware that they did not want such data widely shared. They had mixed feelings on the reminder alarm function and generally felt that the appearance of the devices led to concerns about unwanted attention/questioning and even whether they would use it.

A more recent study carried out semi-structured interviews with eight adolescents and their caregivers. The patients were drawn from a difficult asthma service and had been issued with an EMD for 6-8 weeks (186). Investigators found that experience of requiring urgent, unplanned care and medical treatments had been frightening for both participants and their caregivers. Some participants expressed a perceived role for both preventative medication and healthcare professionals in reducing the risk of this recurring. While some perceived EMDs as playing a role in this, other participants and the caregivers described feeling that the provision of and EMD was a sign that they were not trusted by their healthcare professionals, that they required surveillance and that their healthcare professional was attempting to *"catch them out".* There was an associated risk perceived of their clinical team seeing the data rather than

seeing them. Participants described how the introduction of EMDs may have complicated the process of adolescent users taking responsibility for their asthma, including caregiver concerns around device fragility leading to increased surveillance of their adolescents and the risk of relapse of behaviours following EMD withdrawal.

Finally, in the only qualitative studies carried out for participants who had used EMDs as part of a behavioural intervention study and to date, Foster et al. carried out in-depth, semi-structured interviews with eighteen adult intervention participants focused around their study experience and the acceptability of the EMDs used (184). Study participants found the devices and reminder alarms easy to use (although there were mixed responses as to the role of the reminder alarms). There was a mixed response to their appearance with some participants finding them to be *"bulky"*. As in the previous studies, there were concerns around device fragility and unwanted attention. However, importantly, Foster et al. found that participants perceived the EMDs to be effective reminders for preventer use leading to *"behaviour change and habit formation"*. Some participants further identified the of EMDs role in leading to improving their asthma symptoms and general asthma status. They described a change in their attitudes towards self-management and how it opened

conversations with their healthcare practitioners which they had previously been unable to have. These experiences were not universal. They rather appeared to be linked to baseline attitudes e.g. necessity beliefs and concerns and pre-existing adherence to or dislike of routines. Participants were mixed in how sustained they felt its effect was in the months after withdrawal of the EMD with some speaking about how they would have appreciated using it for longer and others discussing either *"sustained behaviour change"* or being motivated to find new strategies to sustain behaviour change.

6.1.2. Behavioural models of adherence and intervention design

Theories of behavioural change and their resultant models may assist in identifying the behavioural targets for change and pinpointing the mechanisms for behaviour change. This could mean that when interventions succeed or fail, they could aid in identifying how and why, allowing future research to build on that knowledge (187, 188).

In their systematic review, Holmes et al. found that elements associated with the self-regulatory perspective (self-efficacy, necessity beliefs and concerns about medication) were consistently significantly associated with adherence (189). This framework has been used in examining adherence behaviours in asthma. Horne et al. found poor self-reported adherence was

independently associated with doubts about preventer inhaler necessity and concerns about using preventer inhalers (a necessity-concerns framework) (59). Foster et al. in the first study to use electronic adherence monitoring to investigate modifiable beliefs built on this framework, found that adherence was related to treatment beliefs (benefits outweigh harm, concerns about side effects, concerns about safety, necessity of preventer to maintain good control), motivation (the desire to adhere), illness perceptions (asthma as a long-term disease), community support (advice from important others) and routines, again showing strong statistical associations between beliefs and behaviours (54).

Whilst it is generally accepted that behavioural change models are useful for intervention design (35, 187, 189), it is also acknowledged that this approach does not guarantee effectiveness (188, 190). This study sought to use current evidence in this area to aid interpretation of observed findings such that suggestions for implementing behaviour change could be made.

6.1.3. Quantitative worldviews and qualitative research

Approaches towards the conduct of research are intrinsically tied to a researcher's underlying way of seeing the world (also described as a paradigm or worldview). In qualitative research,

engagement with this underlying worldview is seen as a central part of the research process. This thesis, for example, asks whether EMD technology could be used to effectively measure and change adherence behaviours, leading to improved outcomes in asthma. Randomised controlled trial (RCT) methodology comes from a paradigm that expects the answer to such a question can be found (or approximated) through study. This answer can then be generalised beyond the local sample to the population. Whilst hypotheses are neither truly proven nor disproven, they are accepted or rejected on the strength of the evidence. This would be described as a realist paradigm (191).

That poor adherence exists is in itself evidence of a worldview difference between researchers and clinicians on the one hand, and their patients on the other. To the former, ICS reduces risk of poor outcomes in asthma and therefore should be used regularly as prescribed. Clearly many individuals with asthma either do not share this understanding, or do not find this understanding enough to lead to a change in their behaviours.

Denzin and Lincoln define qualitative research as follows:

"Qualitative research is a situated activity that locates the observer in the world. Qualitative

> *research consists of a set of interpretive, material practices that make the world visible… attempting to make sense of or interpret phenomena in terms of the meanings people bring to them."*
>
> DENZIN AND LINCOLN, 2018, P. 10 (192)

One prominent ethnographer further expressed the aim of the qualitative researcher as follows:

> *"I want to understand the world from your point of view. I want to know what you know in the way you know it. I want to understand the meaning of your experience, to walk in your shoes, to feel things as you feel them, to explain things as you explain them. Will you become my teacher and help me understand?"*
>
> JAMES P. SPRADLEY, 1979, P. 34 (193)

This centrality of the individual's experience has the potential to give critical context, depth and colour to both quantitative findings and their application. As a result, although it has previously had a difficult time being accepted as part of rigorous scientific research (192), including in the medical field (194, 195), the employment of qualitative research in answering

questions not suited to quantitative inquiry is increasingly recognised (196).

6.1.4. Constructivism

Constructivism (or constructionism) is a philosophy originating in Piaget's developmental work (197). In their synthesis of paradigms of qualitative inquiry, Lincoln, et al. describe the translation of constructivism into the field as leading to *"co-constructed realities"* and *"co-created findings"* (191, 192, 197). For this study, in recognising the importance of user perspectives to contextualise quantitative study findings and guide future directions, this paradigm was ideal for the following reasons:

1. It recognises participants are not passive objects providing data for analysis but significant actors in the process of creating new knowledge.
2. It recognises that the researcher is less a disinterested external observer, more an individual whose perspective is shaped by their own constructs of reality, allowing this to be taken into consideration in the interpretation of study findings.
3. The use of the interview as a method of inquiry (as employed by this study) is approached particularly effectively from this paradigm.

Where both participant and researcher are recognised as being active in the knowledge-creating process, it is important to acknowledge the issues of generalisability and of rigour. In this study, the approach has been taken to find meaning from what has been expressed in the participant-researcher interaction rather than to summarise participants' perspectives and attempt to generalise to a wider population. In the context of medical research in particular, this could prove invaluable in helping to *"fill in the gaps between theory and practice"* (191, 198). Furthermore, this chapter acknowledges the requirement from a constructivist paradigm for the researcher to be clear on their own role in the knowledge-creation process through reflection.

6.1.5. Choice of the semi-structured interview

To better understand both adherence behaviours and participant experience with EMDs, this project chose to use a one-to-one interview technique. These are generally subdivided into structured interviews which have a fixed schedule of questions, semi-structured which have some fixed questions and ideas to explore but flexibility within the interview to add to these, and unstructured where a few open questions allow the interviewee to determine the direction of the interview (199).

The choice of the semi-structured interview in this study allowed for the best of both worlds, permitting freedom to explore unanticipated ideas and to add clarification where needed (199). In theory, the process of social interaction had the potential to bring down barriers, allowing for greater openness on the part of participants and maximising the knowledge obtained. However, there was also freedom to guide the interview such that the main questions which had been identified as central to the investigation could be explored (199).

6.1.6. Aims and objectives

1. To investigate EMD user experiences of their asthma and its treatment.
2. To investigate EMD user experiences of an EMD system deployed as part of a pilot study of an adherence intervention.
3. To explore EMD user perceptions of EMDs based on their experiences and to understand how this may influence ideas about their future implementation.
4. By drawing on behaviour change theory, to present a working model for behaviour change based on the findings of this study.

6.2. Methods

6.2.1. Sampling

The initial aim was for purposive sampling of 20-30 participants based on self-reported adherence. These participants would be selected from a clinical trial assessing the effect of EMD monitoring with feedback on adherence and asthma control. Recruitment for interview would end when data reached saturation (anticipated at around 30 participants). In the end, due to lower than anticipated study numbers, all participants who attended for a final visit were invited to participate, culminating in a convenience sampling approach.

6.2.2. Interview process

Pilot study enrolment was for six months commencing between December 2016 and December 2018. This permitted participants the opportunity to experience the device and any effects it may have had. Interviews were conducted at the final study visit for each participant by a single interviewer (IA), primarily to allow for the capture of those experiences but also to maximise participation by limiting participant inconvenience, and to combat recall bias resulting from holding the interviews a significant period of time after the study had ended.

The guide was informed by previous work in the area with input from various members of the study team. Questions were

designed to assess participants' experience of their asthma, their medication, their experience of being in the study and their experience of Smartinhalers™. They were also designed to elicit participant responses to potential future uses of EMDs. As implied by its nature as semi-structured, participants were able to direct the flow of conversation, with the questions providing a guiding frame of reference for the subject matter to be covered (200). Follow-up (probing) questions to responses not anticipated in the design of the guide are therefore not included.

The following general topics were covered:

- Discussion of baseline asthma control
- Exploration of baseline medication beliefs
- Exploration of experience with Smartinhalers™
- Exploration of perception of the impact of having inhaler use monitored
- Exploration of experience of feedback
- Discussion of impact on self-management of asthma
- Response to potential future avenues for data capture
- Response to future application/delivery of Smartinhalers™ in the context of clinical provision
- Desirability of Smartinhalers™.

The full text of the interview guide as used in its final version is included in *Appendix E*.

6.2.3. Analysis

In this study, interviews were audio-recorded. This allowed the interview to proceed without distraction and for more accurate analysis (with more avenues for analysis) afterwards (201). Whilst recognising the inherent value of researcher transcription, as discussed in the project protocol, for the purpose of time, this project used an external transcription service. Transcripts were linked with original audio files using the study ID and any identifiable information was removed or anonymised.

A thematic approach was used for analysis. This is a structured approach based on grounded theory that takes data from the collecting stage through to abstraction (202). Its five phases are:

1. Familiarisation
2. Construction of the initial thematic framework
3. Indexing and sorting
4. Reviewing data extracts
5. Data summary and display

Familiarisation (or immersion in the data to enable construction of the initial framework) was conducted in this study by listening to the first three interviews during the initial coding process, conducted by hand. Codes were applied to transcripts and these were then mapped onto A3 sheets. The process was repeated for the next three interviews, using themes emerging from the initial mapping process, allowing for both expansion and refinement as needed. Investigator triangulation (where data were independently examined by two researchers and resultant codes checked for similarity and applicability) ensured that the interpreted themes were grounded in the data.

At the end of this process, an initial framework was constructed. Themes were then indexed separately to facilitate analysis of the remainder of the data. NVIVO versions 11 and 12 (QSR International, also known as computer-assisted qualitative data analysis software) was used to assist the process of indexing and sorting the results of the mapping process (202).

In accordance with Glaser and Strauss's inductive method (202), the next selection of interview transcripts were coded based on the framework. Themes were developed and refined as the analysis process progressed, adjusting the emerging framework to ensure it reflected the accumulating data. Codes were then re-indexed as required.

At the end of this process, further validity checks took place with a repeat process of triangulation. The six initial transcripts were reviewed to ensure that the framework was still relevant. During this process, major codes were extracted from NVIVO into a more visual format and circulated to the wider supervisory team for input. Finally, the last set of transcripts were analysed according to the thematic framework with further theme refinement taking place. Themes were reviewed by two investigators and finalised by consensus.

Even with inductive methodology, there remained the risk of misinterpreting data based on the researcher's own social constructs of reality. There was also a risk of trying to force data into categories that it did not fit. Finally, there was a risk that, in the process of coding and achieving 'higher order' data, these abstractions could become removed from the original, authentic data (203). In order to maximise data validity, investigator triangulation was conducted as described. A rigorous inductive method was undertaken, with data reviewed and re-reviewed, verifying that the thematic framework had been generated from the data. A reflexive statement provided below clarifies the primary investigator's role and voice. Most importantly, this report has included quotes from study participants, permitting them to speak "in their own voice" and

allowing the reader to judge for themselves how well they are represented by the frameworks formed.

6.3. Reflexive statement

As discussed, reflection is an essential aspect to both the qualitative research process and its validity (204-206). Interpersonal interactions varied, influencing the nature of the interview. In all cases, preconceptions about the participant-researcher relationship were present. As the interviews progressed, these preconceptions were challenged, particularly where relating to how natural and authentic the interview process would feel. It also became apparent that some participants had self-stratified into "non-adherent" and "adherent" persons, likely colouring how they projected themselves.

In this study, the initial aim was to minimise the 'researcher's footprint' by limiting the presence of the researcher voice on tape between questions (200). It became rapidly apparent non-verbal encouragement would be an essential substitute and it was explained to participants that these would not denote approval or disapproval (200).

Where misconceptions emerged, awareness of a felt need to be an educator were present (200, 201). There were moments of language barrier – later interviews, for example, demonstrate attempts to steer away from using the expressions "preventer" and "reliever" to describe ICS/LABA and SABA inhalers (201). More subtle were the power dynamics issuing from being a healthcare professional. Attempts were made to mitigate this over the course of the study, e.g. encouraging the use of first names (201).

The initial approach to theme construction was to attempt to summarise what participants were saying. It was soon apparent that there were moments where the recording, the memory of the individual and their progress in the study, the previous conversations that were had were all needed to provide context; and yet faithfulness to the text of what had been said was also required. Over the course of the study, increased confidence was found in using identified themes to avoid the loss of the participants' projected 'selves'.

6.4. Results

Thirty-six participants were recruited to the pilot study. Of these, 30 attended the end of study visit. Two participants were unable to undergo interview (one declined and one was unable to because of time pressures). Sixteen of the 28 participant

interviews were with individuals from the intervention group *(Table 6-1)*.

Table 6-1: Qualitative study – Participant demographics

	Overall	Intervention	Control
Number	28	16	12
Mean age (SD)	43.8 (13.1)	46.0 (13.6)	40.9 (12.5)
Female n (%)	19 (68)	8 (67)	11 (69)
Caucasian n (%)	24 (86)	15 (94)	9 (75)

6.4.1. Summary of themes

Over the course of the interviews, five themes were interpreted *(Table 6-2)*. These related to participants' experiences of having asthma, their experiences of asthma treatment, their experiences of being in the study and their thoughts on potential future applications of Smartinhaler™ Technology. They are explored below, with supportive excerpts throughout.

In the text, participants are identified by their study identification number, the letter C or I signifying their status as either a control or an intervention participant and the letter F or M signifying their sex. This is followed by their age. For example, *"**SIT001IF**, 54 yrs."*, identifies participant SIT001 who was an intervention group participant, female and aged 54 years.

Table 6-2: Themes and subthemes

Themes	*Subthemes*
Theme 1: Participants' experiences of asthma	*Beliefs and attitudes* *Participants' experiences of their asthma symptoms* *Participants' experiences of healthcare services*
Theme 2: Participants' experiences of asthma treatment	*Participants' beliefs about asthma treatment* *Experiences of changes to asthma treatment* *Patterns of inhaler use* *Participants' experiences of using their inhalers in public*
Theme 3: Participants' experiences of the Inhaler Technology Study	*General comments about participating in research* *Participant experiences of using the Smartinhaler™ system* *Participants' comments on study feedback* *Participants' awareness of being monitored* *Acceptability of monitoring to participants* *Impact of the study on awareness and control* *Impact of the study on behaviour* *Participants do not perceive an impact from participating in the study*
Theme 4: Future applications of digital inhaler technology – potential improvements and uses	*Future characteristics of a digital inhaler system* *Views on the nature of feedback* *Views on potential future uses of digital inhalers*
Theme 5: Future applications of digital inhaler technology – desirability, ethics and wider impact	*Desirability of the Smartinhaler™ system* *The subject of data ethics* *Participants' views on the potential wider impact of digital inhaler technology*

6.4.2. Participants' experiences of asthma

Participants' perceptions of their condition, of its aetiology, importance and of their sense of control over it formed the backdrop to their experience of asthma treatment and, consequently, of the study. In this theme, participants explored their experiences of asthma from the beginning of their asthma journey. They also explored how these experiences shaped the ways in which they related to their asthma.

Beliefs and attitudes

Many participants shared stories and beliefs around the commencement of their asthma. Overall participants described three distinct periods of diagnosis. There was an early childhood diagnosis group who generally described their experience of asthma as a *"background"* reality or described prominent early memories of being obliged to take treatment. This was succeeded by a group who were diagnosed in adolescence/early adulthood. A third group described recent diagnoses one or two years prior to entering the study.

For some, their asthma onset seemed to have a precipitating factor. For one participant it was childhood measles. For another it was pneumonia, which he interpreted as being occupation-related. Finally, a couple of participants described their asthma

being complicated by other lung problems, making it challenging to distinguish the cause of their symptoms.

The study sought to recruit individuals with asthma who had suffered a recent exacerbation. Participants therefore tended to contextualise their experience of asthma from this perspective. For some participants, exacerbation was an *"eye opener"* to how serious asthma could be.

> *"I think there isn't enough information on how quickly that can deteriorate… and I guess I also didn't realise how quickly that would affect me as well. So I suppose that scare has changed my perspective on it slightly …"* ***SIT030IM,*** *49 yrs.*

For others the memory of exacerbation provided an important motivation to maintain control. As well as severity, another participant discussed how her perception of asthma as a chronic disease had been challenged through changes in management.

> *"I suppose I probably hadn't really appreciated what a long-term condition was, but now I know … it's not going to go away."* ***SIT003IF,*** *47 yrs.*

Participants generally felt they were in control of their asthma; however, for most this was conditional on how susceptible they were to triggers and how identifiable/avoidable those triggers were. Control was generally expressed as an abstract concept, but occasionally described more practically in terms of the degree to which participants were restricted by their condition.

> *"I would say 80% of the time I feel like I'm in control of it. Because as I say, it doesn't largely stop me doing most things but it can be quite debilitating …"* ***SIT030IM****, 49 yrs.*

Also described in practical terms were the ways participants actively exerted control over their asthma through self-care behaviours. These included being attentive to medication regimes, practising trigger-avoidance or finding ways to improve lung capacity through weight-loss or exercise. Healthcare teams were also seen as contributors, at times key contributors, to good control. For some participants, this came with a sense of surrendering control to their medical team, whilst others described help-seeking as a means of them actively exerting control.

In contrast, some participants expressed perceiving a persistent lack of control. This appeared to be linked to a sense of doing all the right things with no tangible results. For one participant,

this lack of agency appeared to sit side by side with a sense that responsibility for her condition lay outside of herself.

> *"I feel like the doctors should have responsibility over my asthma… I don't feel like they're actually looking into it as much as they should be doing."* ***SIT012IF****, 18 yrs.*

Whilst she was not alone in placing responsibility for her condition with her healthcare team, overwhelmingly, participants seemed to express a sense that they were primarily responsible for their own asthma. They described healthcare teams as being there to give individuals the tools to enable self-care and to support when individuals came to the end of their capacity to control their condition.

> *"Because they're my lungs and I know how I'm feeling, I know my body. And it's my responsibility to make sure that if they're deteriorating or I feel unwell it's my responsibility to contact my GP* and let them know."* ***SIT014CF****, 57 yrs.*

**General Practitioner (GP)*

Participants' experiences of their asthma symptoms

Enrolled participants experienced varying levels of symptoms which changed over time. Some were battling a decline in their condition; others had previously experienced a high symptom burden but were seeing improvement. Some described persistently good or persistently poor symptom control; others described labile symptoms, sometimes limiting, sometimes unpredictable.

Participants defined good symptom control as a lack of reliance on their reliever inhaler (occasionally on their preventer inhaler as well) and the ability to go about their day-to-day activities unlimited.

> *"I've done really well and not seen very many interval symptoms and things like that, so still managing to exercise well and not really having to take my blue inhaler."* ***SIT005IF****, 27 yrs.*

Poorer symptom control manifested as a sense of limitation and escalating healthcare needs whether it be medication or hospital admission. For some, periods of high symptom burden were clearly linked to triggers, such as respiratory tract infections, and were therefore more episodic. For others, poor symptom control appeared unprecipitated and consistent.

> *"I used to be very active, I'd do a lot of exercise, I do boot camp, running, swimming, and as long as I took my inhalers prior to exercise… I was okay. But it's not been working. When I've tried, I've been wheezing before, I've been wheezing throughout, I've been extra short of breath afterwards, so I've thought, I didn't really feel like doing it…"* ***SIT035CM****, 38 yrs.*

Some participants expressed the feeling that, because they had acclimatised to their symptoms, their actual disease control may have been poorer than they perceived. One participant was aware of a disconnect between her actual disease status and her symptom experience and described the role of anxiety in that.

> *"The respiratory team have learned me to remember people do get out of breath and it's not always my asthma and not to panic because that will make me short of breath."* ***SIT014CF****, 57 yrs.*

A sense of frustration emerged from some participants, particularly where symptoms had become limiting, intrusive or

appeared to disqualify them from engaging in certain activities. Some participants also expressed an anxiety with regards to what the future held.

> *"If I'm truthful, I find it, it scares me a little bit because I feel I'm 47 but I'm coughing like a 70 year old and that worries me because I can't actually see an end to it because it feels like it's been a – you know – a slow but sure decline in my health."* ***SIT003IF****, 47 yrs.*

However, a few participants had found a way to utilise their symptoms, describing them as a bellwether for needing to pay attention to general self-care.

> *"Sometimes if I'm a bit overtired or a little bit stressed at work, that kind of thing, it's what I might call a bit of a friend, it's the one thing that tells me that I need to slow down a little bit."* ***SIT030IM****, 49 yrs.*

Participants experiences of healthcare services

Participants described experiences of interactions with healthcare services as either neutral, routine events or with more emotionally charged language. The latter group expressed

concern, disappointment, frustration but also empathy and gratitude. Participants who explored positive experiences in more depth tended to do so on a background of having experienced what they perceived to be good care and a sense of partnership with their healthcare teams on the journey towards better symptom control.

> *"The hospital visit was… a big turn… They've really helped me see that I should keep a better eye on it, than just accept this is how my life is and I'm just going to be a wheezy person for the rest of it."* ***SIT036CF****, 50 yrs.*

Negative experiences were attributed to a lack of knowledge on the side of the healthcare professional, a sense of not having received attentive or personalised care, service pressures and a lack of continuity of care.

6.4.3. Participants' experiences of asthma treatment

A central hypothesis of the therapeutic use of electronic monitoring devices is that they can modify the individual's relationship with their inhaled medication leading to improved disease control. In this theme, participants explored their perceptions of and experiences with asthma treatment with particular focus on these prior to study enrolment.

Participants' beliefs about asthma treatment

Participants had differing experiences of drug efficacy for both asthma medication generally and specifically for preventer inhalers. Perception of efficacy appeared to be intrinsically tied to past experiences for almost all participants. Participants freely attributed a reduction of interval symptoms such as breathlessness and wheeze, reduced frequency of infective exacerbations of asthma, reduced requirement for reliever inhalers, increased ability to exercise, and increased peak flow to the use of preventer medication.

> *"…using the Fostair twice a day has made a huge difference in… I can't remember the last time I used my blue inhaler, I think it was sometime in April, to be honest. That was ages ago which is a big thing for me."*
>
> ***SIT005IF**, 27 yrs.*

For some participants, efficacy was dependent on the choice of preventer drug, its formulation (metered dose inhaler versus dry powder inhaler for example), inhaled corticosteroid dose, addition of adjunct treatment (such as biological therapy) or presence or absence of triggers. The idea of inhalers being only partially efficacious was a recurring refrain. Several participants

described that on a day to day basis, their treatment kept them only just well enough to just function without eradicating their symptoms. For some, such partial efficacy led to a questioning of whether any symptom relief experienced was indeed due to the inhalers.

> *"I don't really know if I notice it working because I take it as a preventer in the morning and at night, I still get symptoms throughout the day so I don't know if I'd get more symptoms throughout the day if I didn't take it."* ***SIT033CM****, 32 yrs.*

Alongside this idea of partial efficacy, one participant also described a worsening of symptoms despite remaining on treatment i.e. a reduction in efficacy over time. Another described an improvement of symptoms such that he had stopped taking his inhaler with little effect, also leading to questioning of its original efficacy.

> *"Well, I stopped taking them and I've not changed. Now is that because I've got better or because they helped me get better? I don't know, there's going to be no proof…"* ***SIT015CM****, 41 yrs.*

Finally, for a few participants, there was no perception/experience of preventer inhaler efficacy.

> *"I still don't feel like they do anything. Apart from obviously my blue Ventolin which does calm it down, but I don't feel like the preventers that they give me do anything."* ***SIT012IF****, 18 yrs.*

Related to the question of efficacy was the question of whether participants perceived their asthma treatment as necessary. Participants, on the whole, defined necessity based on experienced effects of the absence of medication. They feared the symptoms of breathlessness, wheeze, tight chest and fatigue as expected results of missed doses. They anticipated that persistent missed doses would lead to increased reliance on their reliever inhalers. They also feared exacerbation with its resultant loss of function and hospital admission.

> *"I notice if I don't take it, I would definitely be wheezy, my chest would be tighter and then I'll end up having to take it more as a reliever than as a preventer, so it's better to just take it as a preventer."* ***SIT025CF****, 22 yrs.*

A few participants defined necessity in a more positive light, linking it to their experiences of preventer efficacy rather than relying on experiences of missed doses.

> *"Well, because the preventer has obviously largely maintained my breathing and given me a consistent lack of wheeze and all that kind of thing, so generally I find it's essential."*
>
> ***SIT030IM**, 49 yrs.*

A few participants also made a direct link between necessity and being instructed to use medication by their medical team and found this to be adequate justification.

Some participants were more dubious of treatment necessity but were also averse to risking missing doses to prove or disprove this. A significant minority were, however, clear that their treatment – either their preventer or an adjunct – was not necessary, either due to a described lack of efficacy with regards to experience of interval symptoms or on a more theoretical note for one participant who believed his asthma was seasonal and so did not feel there was any need for perennial treatment.

> *"For instance, for six months of the year, they could be completely useless in terms of I might*

not need them at all during the periods where it's good, so summer and winter, I might not need them but it's not a theory I'm willing to test out, if I'm honest!" ***SIT026CM****, 42 yrs.*

Some participants also described a perception of necessity with regards to their reliever inhaler. These participants explained their sense of panic when they had forgotten to carry it and/or a sense of reassurance at its presence, whether or not they were presently experiencing symptoms.

"…because I play a lot of sport, I go to the gym a lot, I play roller-derby, I always have my inhaler with me so that I can do that, so they're my lifeline, I can't be without them. And if anything, if I don't carry my blue inhaler I am actually liable to have an asthma attack because it starts as a panic attack that I've not got it …" ***SIT008CF****, 44 yrs.*

Several participants expressed a sense of reluctance to use asthma treatment and a significant discomfort with their

reliance on treatment or requirement for increased doses of treatment.

> *"…the more you're told that you have to take these drugs and I accept that, I hate it. I hate the fact that I have to, you know, some things are long term but I understand again why I would have to do that…"* ***SIT003IF****, 47 yrs.*

A few participants also described experiences of perceived side effects. For some, dry powder excipient was considered to be the culprit, thought to cause excessive mucus or increase in symptoms. For another, a specific formulation was described as causing tremor. Only one participant linked inhaler use to muscle growth (this participant also described a mistrust of steroids/conventional medicine).

Experiences of changes to asthma treatment

Many participants described changes to their treatment which had taken place over time. For a few, this had been a neutral experience; for others it had not been. Several participants felt that their healthcare teams had changed their treatment regime in order to achieve improved symptom control or to reduce side effects. One participant describes a collaborative decision-making process to her regime change. Whilst she admitted an

element of trial and error involved in achieving stability, other participants described a greater sense of arbitrariness.

> *"I think it varies from doctor or nurse to whoever because sometimes it's a case that they'll just leave you on whatever medications you're on, some are a bit more experimental… I'd been through lots of varying colours of the rainbow…."* ***SIT008CF****, 44 yrs.*

Some participants cited these changes as having had a positive effect; however, for other participants, the changes did not lead to an improvement in symptoms. Another participant described a sense of frustration at the changes. Finally, one participant described experiencing a change in inhaler after having reached a steady state. His response to what felt an arbitrary change in medication was to stop using his preventer altogether.

Patterns of inhaler use

Participants generally described regular inhaler use, often in quite definite terms.

> *"I always used it as prescribed, two puffs in the morning, two puffs at night…"* ***SIT001IF****, 54 yrs.*

A few described a pattern that was more dependent on and responsive to their asthma status. Some participants qualified a description of regular usage as prescribed with admissions of occasional over- and/or under-use. Yet other participants freely admitted to poor adherence, whether regular overuse, irregular use as described below or even absolute preventer non-use.

> *"Probably used it … a few times a week, it depended…"* ***SIT025CF****, 22 yrs.*

Participants also described factors which made them more or less likely to use their inhalers. Participants emphasised the importance of habit formation and cited the role of visual or action reminders such as inhalers being left on the bedside table or in the bathroom so that they would be in view when getting out of bed, when going to bed, when brushing teeth or when taking tablets. Other reminders included important others (e.g. partner), written reminders and mobile phone applications (apps) or alarms, sometimes a combination. For example, one participant described taking her inhalers at the same time as her tablets and having an alarm as a back-up reminder. It should be noted that not all participants felt positively about alarms. One young participant described them as *"annoying"*. She explained that this was due to their intrusiveness:

"…when you've got a weekend off and then it's dinging at eight o'clock telling you to take your tablets." ***SIT012IF****, 18 yrs.*

Some participants cited the importance of factors such as emphasis on treatment importance from the treating team and increasing age and maturity. For others, increased awareness of their asthma as a result of disease progression or of recent experiences of asthma exacerbations was a motivating factor. Several participants cited more than one of these factors, sometimes a mixture between reminders and experiences, in promoting regular medication use.

Less discussed were factors that reduced regularity of inhaler use. Supporting the identification of habit formation as an important part of regular use, participants identified factors which affected routine such as being busy and shift work. One young participant felt that having been an adolescent reliant on her parents to take responsibility for her asthma had been a factor in poor preventer use. For other participants, a perceived lack of efficacy affected motivation for inhaler use.

"…with me I just find if I know it doesn't work, like my Foster when I was on that, I took it

regularly for months and then once they wasn't listening to me that it didn't work, I just got out of the routine of taking it because I knew it wasn't helping me or benefiting me." ***SIT012IF****, 18 yrs.*

Participants also admitted to overuse of inhalers related to triggers (cold weather, viral illness) or the experience of higher levels of symptoms.

Participants' experiences of using their inhalers in public

Generally, participants described taking their preventers at home due to the time of day they were taken. However, whilst not directly impacting on preventer inhaler use regularity, a proportion of participants did express difficulty with using inhalers in public. This uncovered their perception of how others viewed them in light of their condition. It also provided a window into how these perceptions shaped participants' own attitudes towards their inhalers and, ultimately, towards themselves in the context of their asthma.

Primarily, participants complained of unwanted attention. They reported a sense of having to shoulder the burden of how people who had noticed them processed their inhaler use or the fact that they had asthma. A few participants were aware that they were projecting their own views onto others. One described

how, growing up, inhaler use was a sign of *"weakness"* as were other physical attributes such as needing glasses. She went on to admit that whilst she felt taking her inhaler was a sign of weakness, she had noted that others appeared not to have similar qualms.

> *"I see people in the gym, they take their inhalers with them in the spin class. I wouldn't do that."* ***SIT003IF****, 47 yrs.*

Another participant described verbal name-calling he participated in as a child, calling a fellow asthmatic schoolboy *"Darth Vader"*. To him, this appeared to be exemplar of the stigma he now felt, describing asthma as *"taboo"*. Other participants described childhood experiences of being bullied or of asthma not being *"cool"*. They associated it with other causes of shame, such as being overweight. Some participants described their embarrassment as stemming more from a sense of self-consciousness or an anxiety that was not necessarily borne out by experience. One gentleman described his concerns that managers would object to his inhaler use as leading to embarrassment. However when he clarified this with management, they had no problem with him using his inhaler on the shop floor if needed.

For all of these participants, there was a clear sense of wanting to keep their condition hidden. In practice, they described their methods of avoiding attention. Participants would leave meetings and public spaces or delay taking their inhalers (usually reliever inhalers) until there was an opportunity for greater privacy.

> *"I hate it. I always hide behind my mum or someone, or behind a wall and take it. I never do it in front of people, even at work I'll go to the toilets to take my inhaler."* ***SIT012IF****, 18 yrs.*

This sense of embarrassment, whether as a result of perceived stigma or unwanted attention, was not necessarily fixed. For one participant, there was what appeared to be a continuous and co-existent conflict between wearing his inhaler *"almost like medals"* and other times a keen sense of *"taboo"*. Others described overcoming stigma, sometimes as a result of age and habit but also as much by a sense of necessity. These latter participants described having no choice but to become comfortable with their inhaler use and choose to ignore or reframe other feelings and perceptions.

> *"I think just me getting older, honestly and just not really caring! Realising that my health is important and many people have asthma and*

actually, no-one really cares if you have an inhaler or carry it around or take it out in public." ***SIT025CF****, 22 yrs.*

Finally, this sense of stigma was not by any means universally shared. Several participants stated that public inhaler use had never been an issue. Encapsulating the feeling from this group of participants, one simply stated,

"I've never had a problem with using inhalers in public. If you need to breathe, you need to breathe." ***SIT008CF****, 44 yrs*

6.4.4. Participants' experiences of the Inhaler Technology Study

Participants' experiences of the study were influenced by their beliefs and experiences before the study, their understanding of research, motivations for participating in research and their experiences in the study itself. The first two themes explored pre-study perceptions. This theme elucidates some of the within-study experiences, which had potential to shape participants' views of the technology and even modify their prior held beliefs.

General comments about participating in research

Participants described being motivated to take part in the study out of a general desire to contribute to knowledge about asthma, to raise awareness about environmental pollutants as triggers and to help other people with asthma understand the benefits of using their medication as prescribed. For one participant, her motivation for raising awareness about how serious asthma could be came from an even more personal experience of bereavement.

> *"…my sister died when she was 34. She had an asthma attack and died and it was really important for me to understand and to contribute to this because I think other long-term conditions or horrible diseases get a lot of air space, asthma doesn't."* ***SIT003IF****, 47 yrs.*

On a different note, one participant explained that her motivation for taking part in the study stemmed from having previously noted that the accountability of participating in research had reduced her likelihood of smoking.

Participant experiences of using the Smartinhaler™ system

Where described in general terms, participants generally described the Smartinhaler™ devices as *"good"* and, less

commonly, *"helpful"*. A couple of participants spoke of the appeal of trying out a new technology for its own sake.

> *"I think it's quite cool. It's quite fun having something on your inhaler that lights up…"*
>
> ***SIT008CF**, 44 yrs.*

The devices' physical characteristics drew a variety of responses. Some participants saw them as bulky. This was at times positive (better inhaler grip, increased inhaler use awareness), others described acclimatising to it. Some stated that they did not find the devices bulky or intrusive or find that they affected use of their inhaler or spacer. For several, however, the perceived bulkiness was a significant negative. It affected how effectively they felt able to use their underlying inhalers, creating a perception that they were harder to carry around, harder to use or more embarrassing to use in public.

Other physical characteristics which were highlighted by participants included the presence of the light-emitting diode (LED). Some participants found this to be a factor which helped them to engage with the Smartinhaler™ system. For some participants, the nature of the device as attached to the inhaler meant that they had to be particularly conscious to prioritise

only using inhalers with the device attached. They admitted that this was not always possible.

> *"Making sure I always had the inhaler with the device on, that was a little bit awkward, because I have inhalers dotted around in every handbag, everywhere, and it's thinking, "No, I need that one", but that was all."* ***SIT031IF****, 50 yrs.*

Participants variably noted that the devices were easy or difficult to attach and detach. The devices were reported to be easy to recharge and, on the whole, did not need recharging as frequently as expected (they had been instructed to recharge weekly). Some participants used the app as a guide to when the devices needed recharging rather than regularly charging at a set frequency. Not all participants, however, recalled that the devices required recharging.

With regards to the app, some participants complained that the original process of downloading was complicated. Participants described problems with connectivity, generally between devices and the app. They described needing to re-synchronise the device and the app on multiple occasions.

> *"Temperamental would be one. Other than that, when they work they're good but when they don't it is a bit of a nightmare having to keep syncing them up all the time."* ***SIT009IF****, 34 yrs.*

Participants were split over how easy the app was to use, with some finding it straightforward and some even finding that synchronisation was occurring automatically. One participant found the device's general acceptability was balanced against the battery drain he attributed to using the Smartinhaler™ system. Another, however, described the app as not taking up excessive amounts of room on her phone such that it could interfere with her phone's usual functions. One participant noted that the battery LED proved an inaccurate guide to remaining battery life.

In some cases, participants further volunteered a frustration with the reliability of the system, generally relating to delay in recording inhaler actuations. For a few participants, there were issues with the app picking up inhaler actuations unrelated to whether or not it was synchronised. Some participants noted that there were actuations which did not register at all. One participant noted that there were spurious actuations and another that there was cross-talk between the two devices

resulting in actuations taken on the preventer device registering as also taken on his reliever device. Of the participants who noted such issues with reliability – whether due to a delay in registering actuations or not registering actuations at all, some described a sense of frustration and annoyance – particularly when it was felt that there was a sense that the system was misrepresenting their inhaler use.

> *"…there were connectivity issues so I wasn't really sure that all the registered puffs were going through and things like that. Sometimes I would've taken eight puffs and it might show five, and I don't know if that was because it wasn't picking up or because it wasn't synching correctly. I stopped trusting what I was seeing there."* ***SIT013IM****, 28 yrs.*

This particular participant went on to describe a gradual disengagement with the study.

Other participants also discussed how engaged they felt with the Smartinhaler™ system. This was generally split along the group allocation (i.e. control versus intervention).

> *"…it just said 'Smartinhaler', it didn't really tell me much…"* ***SIT014CF****, 57 yrs.*

"…when it was working and I could see how it was supposed to work, I thought it was very clever and plenty of information there."

***SIT017IM**, 58 yrs.*

Participants' views on study feedback

Participants identified three aspects as to what they felt was study feedback: the questionnaires, the feedback conversation, and data from the app. For control participants, only the questionnaires and a one-way update from participant to investigator were available. Consequently, in their evaluation of study feedback, control participants in general spoke about a lack of intrusiveness in arranging and participating in the interim appointments and varying degrees of helpfulness (or lack of) of the questionnaires.

"Some of the questions I think were stinkers, for me ambiguous, which could have been worded better so I don't know how it's going to reflect…" ***SIT015CM**, 41 yrs.*

Although not universal amongst control participants, those who did find the appointments helpful shared with intervention participants a sense of increased awareness of their condition.

"I suppose, I found it useful in trying to… just sort of gather my thoughts myself of how… my

asthma's been controlled for the last two weeks or the last month; because I suppose because I've had this condition since I was a young child, you take it for granted and I just accept it, it is what it is, without necessarily thinking about keeping it under control or triggers or things that maybe happened with it, or how I feel about it, so yeah." ***SIT035CM****, 38 yrs.*

Generally, for intervention participants, and for an occasional control participant, there was an appreciation for having clinician contact over and above their usual asthma follow-up. For intervention participants, this allowed for further conversation and so these participants tended to talk less of the frustration of the questionnaires' rigid wording. Intervention participants also used the appointments as an opportunity to discuss issues around the Smartinhaler™ system's functioning and reliability.

"I liked having the regular phone calls because it gave me someone to speak to about my asthma in a way… like I say, I can't really speak to anyone else about my asthma so having someone there to tell me how it's going

and how my asthma should be, about my inhalers, it helped a lot." ***SIT012IF****, 18 yrs.*

Participants' awareness of being monitored

Participants were generally aware that their inhaler use was being monitored, irrespective of whether or not they were intervention or control participants. During the process of consent, all participants were informed in vague terms of the function of the Smartinhaler™ devices, that the devices would collect 'patterns of inhaler use'. Some participants recalled these terms, discussing collection of *"patterns"*, *"readings"* and the provision of *"data"*. Others were clearer in understanding that the device *"picks up exactly how many dosages I take"*. Of particular interest was just how clear some control participants were on the purpose of the devices despite only having had minimal information to start with and not having the reinforcement of regular device or investigator feedback during the course of the study. One described the Smartinhaler™ system as being *"like Big Brother watching me"*.

"Basically, every time I use my inhaler, it stores my information and then at the end of the research programme, you guys will check my results out and see how often I've needed my inhaler and how bad my asthma is and then

from there, you guys will see what other methods you can do to help me with my asthma." ***SIT006CF****, 27 yrs.*

Control participants also described the light flashing as a marker that their adherence was recorded.

Some participants did find that their awareness of being monitored reduced with time. Others found that, having previously reduced with time, their awareness was re-triggered by illness. Still others described trying to deliberately ignore the fact that their inhaler use was being monitored.

"…If I'm brutally honest, I just kind of almost preferred to keep taking it as normal… I didn't want to know if you follow me, pick up on my right wrong and any indifferent practices that I had." ***SIT024CF****, 39 yrs.*

Finally, some participants perceived additional information as having been recorded that was not actually collected such as symptoms and location.

<u>Acceptability of monitoring to participants</u>

Participants expressed that the acceptability of monitoring was intrinsically linked to its purpose in improving asthma within the

context of the study. Some described being suspicious of data collection as a principle but accepting it for the sake of research.

> *"If it was anything else that was being monitored, I would be bothered but because it's of a benefit to me and other people, I don't think it bothers me at all."* ***SIT002CM****, 57 yrs.*

A couple of participants described being wary of the research team being able to see when they were not adherent but that they acclimatised to this with time.

> *"At first, I wasn't too keen because I was first thinking what if I mess it up, am I going to stick to it properly because I use my inhalers in the morning and the night but then I got a new asthma technique where I've had to use it in the afternoon, I thought to myself am I going to keep up with it? But then since I've started becoming more ill, I've had to stick to it and to be honest I've got used to it, at the beginning, everyone goes through that phase where "no", but once you're into it, you're into it."* ***SIT006CF****, 27 yrs.*

Others, however, specifically stated that they did not feel their privacy was affected. Some were further able to describe the

idea of being monitored as an actively positive thing. For these participants, it was *"reassuring"*, it increased their sense of self-esteem and it helped provide them with a record of their own inhaler use, both for self-monitoring and for having objective data to aid communication with their clinicians.

During the interview, some participants were asked hypothetically whether their acceptance of monitoring would have been different had it been covert. In general, their response did not become more negative. An exception to this was one participant who suggested that covert monitoring would cross a line, although also stated that he understood that in the context of research a control group is necessary. Interestingly, one participant expressed discomfort less directly.

> *"I don't suppose you'd be very impressed if you were monitored and you didn't know. I don't know that I would mind, personally, because, why? I haven't got anything to hide. But I suppose some people would get quite cross about that."* ***SIT029CF****, 49 yrs.*

Impact of the study on awareness and control

Participants did not express any particularly large shifts in how they perceived their inhalers from participating in the study but

a few did identify the study as reinforcing their importance. Similarly, participants – both control and intervention – noted that participation in the study, awareness of being monitored or the device or app increased their awareness of how they used their inhaler in terms of timing, frequency and adherence.

> *"I think sort of being in the study has made me think more proactively about taking my inhalers and about my Fostair and when I'm using it and making sure I am using it at those regular times and not forgetting to do it, not like going to bed at night and falling asleep before taking my inhaler and things like that, so I think it's been really helpful in that respect."* ***SIT005IF****, 27 yrs.*

A more specific awareness benefit of the Smartinhaler™ system for intervention participants who could not remember whether or not they had taken a dose was being able to check the app for confirmation. Whilst unanticipated, a few intervention participants also reported finding the alarm function on the app and activating it, further increasing awareness of when they needed their doses.

In addition to increased awareness of treatment use, participants widely reported increased awareness of their own asthma status, including their symptoms and its general

importance as a condition. Whether well or poorly controlled, participants had learned to live with their symptom level. They took good control for granted or acclimatised to poor control, no longer recognising it as such. Increased awareness was particularly attributed to the questionnaires (as already discussed) and also to the reliever Smartinhaler™ (particularly, as noted by the control participant below, its LED light).

> *"It was a bit of a shock when I first started using them and I'd sync them and I'd go on to the app and it's like I'd used 170 in seven days and that's just on my blue one."* ***SIT012IF****, 18 yrs.*

For a few participants, this ability to self-monitor and the resulting monitoring feedback provided an increased sense of control over their condition, or at least the hope that their symptoms could improve. In this context, the study not only increased their awareness of their asthma status but also caused them to consider its emotional effects. This level of mindfulness sometimes led to an appreciation of how well controlled they were. It sometimes also heralded potential for changing behaviour as expressed below.

> *"…the device, because it's flashing, I'm seeing how many times I'm using the inhaler because obviously it flashes, you don't forget it because it's such a bright colour so I know when to go to the doctor's and when I need medical help."*
>
> ***SIT006CF**, 27 yrs.*

For some participants, conversations with investigators helped them have a better understanding of asthma at a more general level. One participant described appreciating the opportunity to discuss the links between upper airway and lower airway atopy. Another simply felt impacted by the knowledge she was not alone in her condition.

For a group of participants, there was a sense that the study impacted how they felt about using their inhalers in public. One 47 year old participant began by describing how her underlying dislike and avoidance of public inhaler use had not essentially changed. However, she then went on to explain how she had found herself showing her colleagues her inhalers with the devices attached – behaviour which she described as *"bizarre"*. Thus, for some, the increased public attention was a positive, raising awareness of a condition that was important to them to

speak about. For others, it was a significant negative however, increasing their already-existing sense of embarrassment.

> *"That puts you back a bit because people are looking at you… I find it embarrassing getting the inhaler out… but on top, because there's a device on top of it, it's even more embarrassing…"* ***SIT006CF****, 27 yrs.*

Impact of the study on behaviour

Several participants described changes in behaviour resulting from participation in the study. These included increased confidence asking for help and subsequent increased help-seeking behaviour. Some described increased preventer use, increased use of inhalers in public and more intelligent preventer use e.g. spreading out doses to increase proportion of time covered. With regards to relievers, participants described increased reliever carriage (although this was not universal) and decreased reliever overuse. Finally, some participants felt more informed about their triggers and more consciously practised trigger-avoidance.

In addition to directly impacting participant behaviours, a key study aim was to assess whether the use of the Smartinhaler™

System had any impact on intervention participants' treating teams. Only a few participants described this having happened. Where they did, the effects they noted included responses of both cynicism and interest. One participant described how her Practice Nurse felt a sense of having reached the limit of treatment options irrespective of the data. However, some described improved communication due to the presence of objective data and even changes in medication regimes. Whilst it is impossible to surmise whether or not the changes in medication regime would have taken place without the study, participants appeared to attribute the data to having played a role in decision making.

> *"She [the Practice Nurse] saw that because I was using the Bricanyl more than they would like, it suggested a change to my routine so I went onto the MART routine instead of using the Bricanyl."* ***SIT021IF****, 50 yrs.*

> *"Like I say, I've been on the Fostair for ages and it wasn't until I had the app and I went in and showed them, until they started trying me on new things so it did help me in that way."*
>
> ***SIT012IF****, 18 yrs.*

Finally, some participants described changes in behaviour which were not intended by the study. The most common of these was that participants described having to be conscious of which of their inhalers had the study devices attached and took extra steps to ensure that they used that particular inhaler. Others described occasions when they were unable to take those steps, in which case their data was not recorded for those particular actuations. Other participants described it changing how they interacted with their inhaler, for example, using their inhaler with two hands to make sure every actuation registered or compressing device clips (which detach the device) every time their inhaler was used. One participant described not performing the priming dose on the commencement of a new inhaler to avoid actuation data inaccuracy. Of more concern, a 60 year-old male participant described how had elected to leave his inhaler in his locker when he was at work as he felt it was too bulky to keep in his pocket.

Some of these changes were, however, positive. One participant described how the pre-study change in formulation from dry powder to aerosol improved his control. Finally, a small number of intervention participants identified how to use extra features on the app such as peak flow recording and reminder alarms.

Participants do not perceive an impact from participating in the study

Not all participants perceived an impact from being in the study. Some participants felt that it impacted their awareness but not their behaviour. With regards to inhaler use behaviour, some participants who perceived this lack of impact explained that they had been taking their inhalers regularly prior to the study. The implication from them was that there was no requirement for behaviour change.

Similarly, when asked whether there was an impact on their asthma control, some participants responded that there was either a perception of no impact at all or an impact on awareness of asthma status but not on the condition itself. This sense of lack of impact was also attributed to baseline status or factors outside of the study's control, a sense that their particular condition was, as it were, outside of the study's jurisdiction, either because their control was too poor or, indeed, stable prior to the study.

> *"I probably wouldn't say it has in that respect because like I say, I'm still on trial and error at the minute with the doctor's, so my symptoms are always going to be bad until they can find something that suits me well."* ***SIT012IF****, 18 yrs.*

For other participants, the study's lack of impact was due to intrinsic study factors such as how well the Smartinhaler™ system functioned, the study's duration and the fact that the study was not a drug study.

> *"…but I'm not going to say it cured me, there was no special medicine you gave me. It was totally un-invasive…"* ***SIT015CM****, 41 yrs.*

Finally, some control participants identified the lack of feedback as a factor for lack of impact.

> *"If I saw the results from it, because I'm quite mathematically minded and I do like a spreadsheet and a chart, if you were seeing your own results out of it, so you had access to that information, then I think you probably would feel more in control because you could see exactly what time of day you take your inhalers."* ***SIT008CF****, 44 yrs.*

It should be noted that a number of participants expressed a perception of lack of impact but then went on to describe cases of impact. One participant explained the complexity of trying to

attribute behaviour change to a research intervention at an individual level.

> *"I don't think the study has been, I can't think of the word but I don't think it's been part of my self-control. Yes, it prolonged the usage of the inhalers which then allowed me to gain control but without research, would I have still been taking the inhalers? Quite possibly."* ***SIT015CM****, 41 yrs.*

6.4.5. Future applications of EMD technology – potential improvements and uses

The final part of the interview asked participants to give their responses to potential future iterations of and uses for this kind of technology based on their experiences of asthma and of being in the study.

Future characteristics of a digital inhaler system

Physical characteristics

Physically, some participants felt that the devices needed to be easier to attach and detach. Several also felt that they needed to be less bulky, for example having smoother edges. Others suggested designs that could appeal to younger and male users.

"I know, not from me but from a male side, a young male side, they don't want pink inhalers, it's not right, it's not cool, so maybe jazz them up a bit …" **SIT011IF**, 46 yrs.

One participant suggested that rather than having the chip embedded into existing inhalers, digital inhaler devices could operate more like a canister sleeve, similar to the earlier models of the Smartinhaler™ system. There was a general consensus, however, that integrating a digital inhaler system such that it was incorporated into existing inhalers rather than attached to them was a good idea. Some concerns about such technology were also expressed. These were related to the financial and environmental costs of having extra disposable chips embedded into every inhaler.

"You just need to think about how environmentally friendly it is because obviously at least with it just being something you clip into, you're going to use that for as long as it is still working rather than throwing away mechanics every couple of months when you finish an inhaler. I'd rather not be wasteful."

***SIT008IF**, 44 yrs.*

App and general platform

With regards to the platform, an expectation that future devices would prove more reliable recurred. This was expressed strongly where participants felt the data produced during the study had poorly reflected their actual inhaler use behaviours, delayed data synchronisation, or simply did not function with their phone's operating system.

> *"I think the main problem was the data link didn't work! That's the very obvious thing, if it doesn't synch with the phone, then it's useless, both from the patient's point of view and for anyone gathering data, that's the one thing that has to be most clearly sorted out before it's implemented on a wider scale."* ***SIT001IF****, 54 yrs.*

More generally, the same participant also suggested softer in-app wording.

> *"'Adherence' sounds a little bit… It didn't bother me but I guess some people might, if it was sort of termed in a more friendly way, that might help some people…"* ***SIT001IF****, 54 yrs.*

Other participants suggested that, when the app detects non-use of inhalers, a reminder notification with or without alarm could be activated. A diary function for if the app failed to record data or means of notifying the user that there had been a device malfunction were also suggested. One participant suggested an in-app guide to pairing the app and device.

For some control participants, the ability to see their own inhaler use data was felt to be useful. Similarly, for some intervention participants, more granular data such as the ability to see actual time stamps (rather than just an am/pm division) was felt to be useful. Practically, several participants suggested a notification to warn when the canister in use was close to needing replacement.

Collection of trigger data

Participants anticipated the usefulness of a platform that would integrate inhaler use data with trigger data such as pollen counts or with additional information from the user such as their asthma plan or a symptom diary, with the potential to deliver notifications on impending appointments.

> *"…there is potential to have far more stuff on there in terms of self-care and flagging and things like that and maybe a bit of narrative, so*

you've got feeding back to you, "this has come up, have you thought about ..?", so just having those red flags or that advice…" ***SIT003IF****, 47 yrs.*

Similarly, a control participant noted that a time stamp would allow for cross-referencing with other wearable health apps to relate activity and inhaler use.

When asked about other avenues of data collection to increase the impact of the Smartinhaler™ platform, there were a range of responses. A few participants expressed concerns around potential impact on privacy or expressed a lack of interest based on a perceived lack of potential impact on their own asthma.

"What would be the benefit of that though? That would be my question. I know my triggers so I wouldn't feel like I needed it to be linked to them…" ***SIT025CF****, 22 yrs.*

Most participants, however, felt some level of trigger data collection and/or mobile health (mHealth) data linkage would be useful. Environmental suggestions were pollen, weather (including humidity and temperature), pollution and notification of local respiratory infection outbreaks with some volunteering location tracking as a means of personalising this information. Physiological markers included heart rate, lung function (FEV_1

as well as peak flow), oxygen saturation and other stress markers. Other automated inputs suggested included step counters and night-time wakening. Finally, user-determined inputs included symptom diaries, asthma control questionnaires, non-inhaler medication use e.g. nebulisers/OCS, allergy profile, dietary profile, smoking status and presence of other chronic diseases.

Uses for such data collection included being able to track whether increased reliever use was linked to particular environments (e.g. high pollen), activities (e.g. exercise) or circumstances (e.g. stress).

> *"… if you could track somebody's movements all round, you could see where they've been, what the weather was like and you'd probably understand the symptoms of asthma better and why they get asthma and why they don't get asthma…"* ***SIT002CM****, 57 yrs*

Other suggestions involved using lung function, night-time wakening data, symptoms or medication diary to record and monitor asthma status. One participant wondered whether such a platform would allow people with asthma to gauge where their levels of exercise were in relation to what would be expected for their level of severity.

Participants also posited that such data could be used to identify and evidence triggers where not previously known. This could empower users to take preventative measures including avoidance, ensuring their reliever inhaler was on their person, and prophylactically taking their antihistamines. Participants suggested that a platform linked to other wearables could permit early recognition and rescue either using physiological markers like heart rate or lung function to advise reliever use or even seeking medical attention.

> *"When you were saying about the Fitbit and things like that, I did wonder about heart rate target zones then and triggers for when you need to take your reliever…"* ***SIT013IM****, 28 yrs.*

Other participants suggest that such a platform could monitor the physiological response to treatment e.g. heart rate response to SABA use. Finally, one participant suggested linking in such a platform with National Health Service (NHS)-provided advice regarding asthma.

Global positioning system (GPS) acceptance

If environmental data collection is to be tailored to the user, the use of location data (GPS) needs to be considered. This question

was therefore posed to participants and elicited a range of responses. A sizeable number of participants were unconditionally accepting of its use. As several participants noted, their smartphones and many of their mobile applications already employed location data. A few participants expressed that acceptance of such data collection was conditional on guarantees of data security as well as the ability to opt-out and turn off location tracking when they did not feel it would be of relevance to their asthma. Some participants appeared more hesitant in their acceptance, generally expressing this by stating that others may find the idea more difficult.

> *"Some people are paranoid! [laughs] You know, the Big Brother scenario. Yeah, I'm never anywhere I shouldn't be! It doesn't bother me who knows… well… yeah… it doesn't bother me but I could imagine it might bother some people!"* ***SIT001IF****, 54 yrs.*

For a few participants the idea of GPS tracking was not acceptable and was even described as *"invasive"*. One participant articulated the ethical issues at play.

"Yes, it's where you start to stray into why that's important which I suppose if you're looking at weather or pollen or environmental factors, that it would be but obviously a lot of asthmatics carry their inhaler with them at all times… that gives you access to quite a lot of information about somebody that is irrelevant to their healthcare and, like a lot of things, you would want some assurance that it was being used properly…" ***SIT026CM****, 42 yrs.*

Views on the nature of feedback

As part of the study, participants had a monthly telephone call either just to collect asthma control/quality of life data for controls or also to feedback inhaler use data for intervention participants and discuss whether this suggested need for further medical input. This was taken as a base experience from which to ask participants what they felt such feedback should look like if a digital inhaler system was employed in routine care.

Content-wise, one participant responded that she would like a record of her questionnaire responses to self-monitor her

asthma status. Some control participants mentioned that they would have liked access to their own inhaler use data.

> *"Oh, I want to see charts. I would love my… if you could link into it. Like you've got the app on the phone at the moment, if that came up and almost like your health apps that you get on your phones now, if it just gave you a chart that explained what was happening when and you could see your own trends and information, that would be dead cool, I'd like that."* ***SIT008CF****, 44 yrs.*

Others suggested a record of lung physiology data (such as spirometry), again as part of self-monitoring. Participants suggested a platform that could offer support based on inhaler use, for example signposting to relevant self-management advice. For other participants, the capacity for unstructured conversation remained an important part of the feedback process.

Participants' feelings on how frequent such feedback should be tended to be related to their own underlying asthma status and how frequent their own healthcare service use was.

> *"Probably as and when you need it, I don't think if your asthma is on an even keel and you're relatively okay, you probably don't really need any feedback, it's maybe if you're becoming poorly and it looks like … you're having a flare up, then that's when they should probably be contacting you."* ***SIT021IF****, 50 yrs.*

For participants with milder asthma (even if known to the hospital), incorporating such feedback into the annual or biannual asthma review with an option for expedited review if a problem was remotely detected, was adequate. Hospital patients tended to focus on more regular reviews (e.g. monthly, six-weekly, two-monthly, three-monthly or three-to-six-monthly).

> *"I see my doctor probably most months, about something, sometimes it's a couple of months but yeah, it's probably about every six weeks maybe, when you're someone that has got quite a few health problems, especially if you're not dealing with it very well … so probably every six to eight weeks you need to see somebody."*
>
> ***SIT027IF****, 58 yrs.*

One primary care patient discussed regular appointments similarly to the secondary care participants. Of interest, some participants saw the potential for technology to play a direct role in feedback, for example monthly prompts through the app or texted feedback with the option for an appointment only if required rather than a fixed regular appointment.

> *"…if you were going to have prompts on the app, maybe as and when it happens, obviously that's not always able to happen when it's a person, maybe as it was being done on a monthly basis, just to check in "Is everything okay?", and then if there's any issues, discussing them through then or being able to discuss the issues as they arise, if they're more pressing…"* ***SIT005IF****, 27 yrs.*

Participants variously suggested uses of technology which would mostly replace face-to-face interactions with clinicians or support existing interaction. Several were keen to keep, at a minimum, their annual or biannual asthma review. This would be an opportunity to discuss the data in greater depth and fit them into the context of an outside view of the user's asthma status, making them more personally relevant to the user whilst

using them to modify management. The risk of not having a face-to-face conversation was felt to be that users may be unable or unwilling to communicate their full asthma status remotely, giving clinicians only a partial view with which to propose updates to management.

> *"Personally, I'd be quite happy to do it digitally but then I think you still need to have a physical face-to-face meeting on a regular basis, six-monthly or 12-monthly. But then, as I say, that information would actually inform that review much better than just doing an on-the-spot peak flow and blood pressure and asking you how you've been and then they look to see if you've had anything different prescribed or whatever and then off you go for another six months."* ***SIT030IM****, 49 yrs.*

Most participants expressing a preference for face-to-face reviews were open that this was a personal preference.

> *"I'd prefer face to face because that's how I like doing things, I don't like sending emails, I'd rather phone someone up because it's personable and you don't get any*

misinterpretations and if you do, they're eradicated there and then." ***SIT015CM****, 41 yrs.*

Many participants were happy with at least an element of feedback being remote, generally via a telephone call supported by email or text. Video-call was suggested as a way of remotely facilitating face-to-face feedback conversations. Some participants suggested that the mode of feedback would depend on the patient. For elderly patients or non-adherent patients, face-to-face clinician appointments were suggested. Text messaging was a suggestion for users with milder, more stable asthma.

The majority of participants felt that feedback should be coordinated by the primary care practice, whether GP or Practice Nurse. A few participants saw a role for the hospital if a patient was under hospital care and for two participants, hospital care in the form of an Asthma Nurse Specialist or consultant respectively, was preferable to primary care.

"Consultant-wise, it depends though who's the GP because if they are just new to the surgery or new to the job, I wouldn't feel very comfortable with it because they wouldn't know

the situation I've been in and where I am right now, whereas consultants, because obviously they see asthma patients constantly every day, so do that, I wouldn't mind, it's just that GP wise I wouldn't feel comfortable with." ***SIT006CF****, 27 yrs.*

Where participants gave a clear reason for preferring their primary care clinicians, there were expressions of the fact that there was a pre-existing relationship, that their healthcare providers knew or had access to information on their background and that they would go on to initiate and continue management.

"…when you go to the doctors you kind of talk about everything and they already know you. And because I've used this particular doctor's surgery on and off since I was 11, they kind of know you and they've got your background … So, you're more comfortable with them and you're more happy, I think, to talk about how you're feeling and perhaps how different things are going on with your health." ***SIT008CF****, 44 yrs.*

Most participants expressed a desire for joint responsibility to self-monitor with their chosen clinicians. The clinical team's role

would be first to support the user in interpreting the data in a way that would have meaning to them, potentially within the context of the asthma review and then to support in placing this in the context of their asthma management where, for example, changes to lifestyle or medication regime were needed.

> *"Well, I should be responsible for keeping my eye on it, it's my body, it's my asthma, so I need to know what's going on first and then if something's happening then I could probably say, 'Right, well if it's connected with any of them' then I could just say, 'This is what's been happening' and you can just have a look and, but I'm responsible for my asthma really.*
>
> ***SIT011IF**, 46 yrs.*

Participants were asked about the acceptability of a tailored lay service providing feedback. This was more divisive. Several participants cited concerns around lack of relationship and their own unwillingness to provide access for such a service to view their medical records to provide the necessary background information. Participants worried that, without clinical training, such a service would be able to do little more than signpost to clinical teams or provide technical support. Others worried

about the potential for provision of conflicting advice between such a service and a patient's usual healthcare providers, leading to confusion for patients.

> *"I'm not sure I'd want a call from a call centre, some private company giving me a call and saying, "You've not used your inhaler properly this week!" I don't think I'd like that at all!"* ***SIT026CF****, 42 yrs.*

In terms of duration of device supply, there were three main camps. The first camp placed decision-making in the hands of the providing clinician and the potential user.

> *"…that would sort of depend on the agreement between a doctor and the person with asthma, as to what's best for that person at that time. Anything between a couple of months to a year, to cement it into somebody's life."* ***SIT005IF****, 27 yrs.*

The second camp was clear that, because of the seasonal nature of asthma, the duration would need to capture all four seasons; therefore devices would ideally be supplied for a minimum of one year. A third group of participants advocated for long-term

or permanent use of the system to cover, not only environmental changes, but changes in asthma status that occurred with time. A few participants had no strong opinions

> *"…so long as there's a justification behind how long and … you have a choice…"* ***SIT026CM****, 42 yrs.*

Views on potential future uses of digital inhalers

Participants were directly asked about some potential data usage scenarios (see figure below).

Figure 6-1: Excerpt from interview guide

How would you feel if your GP or consultant/another healthcare professional/a non-healthcare professional:
a. Discussed the data they had obtained from it with you?
b. Asked you to change something based on this data?
c. Carried out an emergency intervention based on this data?
d. Used it to monitor your response to treatment?
How would you feel about this data being used to inform what treatment you are/are not prescribed?

Participants were clear that they would want the opportunity to have their data discussed with them. They were at times more dubious of having to change their behaviour on the recommendation of their healthcare team in response to the

data. Most participants were, however, open to this so long as there was a joint decision-making process. Similarly, all participants who responded to the question felt that monitoring response to treatment was a good use of the data.

The question of emergency intervention was less straightforward. For some participants, there was a sense of losing control of decision-making to their clinicians. Others felt that emergency help should depend on the degree of intervention – a phone call or in-app alert were generally acceptable. Only a few participants were open to the possibility of the more extreme intervention of an ambulance being sent. Participants more accepting of this tended to have severe asthma, a history of multiple admissions or live alone. Some participants suggested that the intervention would need to be personalised to the user, for example, by taking into account their usual patterns of inhaler use.

> *"I think the number's really low but if you have like five or six puffs of your blue inhaler or something, that's enough and you should be going to A&E. I could have that for breakfast sometimes so it depends, if you're going by government guidelines, they'd probably intervene …"* ***SIT033CM****, 32 yrs.*

Another suggested that there should be a way of cancelling a planned intervention.

> *"I think you'd be embarrassed if an ambulance came though, you know what I mean, and you didn't need it. There need to be some sort of, yeah, there needs to be something on the app that says, 'It's fine, it's ok, I don't need you'."*
>
> ***SIT029CF**, 49 yrs.*

Most participants were accepting of the use of digital inhaler technology as a means of assessing suitability for treatment escalation (in the posed scenario, biological therapy). Participants who expressed concern about this generally did so from a personal standpoint. One young participant noted that she has benefited from her biological therapy and that, were it stopped because she had not met the adherence threshold, she feared she would be at high risk of deteriorating. Another severe asthma clinic patient had experienced issues with device reliability during the course of the study and questioned whether the devices were reliable enough to base such decisions on. Another participant questioned the fairness of such a proposed use and noted that being declined treatment on the basis of an arbitrary adherence cut-off might be

frustrating for the patient who had treatment escalation declined. Importantly, one participant noted that some people with asthma who are poorly adherent are also high risk.

> *"… but if you're the sort of person that has chronic* asthma and you've had it since you were a child and it's stopped you doing anything then you're going to be annoyed with it and you're not always going to want to do what you're supposed to do and you're not always going to want to do what you're told. So, I guess it would depend on the type of patient you were talking about…"* ***SIT029CF****, 49 yrs.*

* ***SIT029*** *used the word "chronic" as a marker of severity rather than time-course*

Participants felt that the data would provide their healthcare teams with more detailed, accurate and objective information on their asthma status that would enable better-informed decision-making and management.

> *"Like I say, it shows that you're not lying then and that actually it's there, it's in black and white, you can see that I'm struggling."*
>
> ***SIT012IF****, 18 yrs.*

Participants were keen on data being used for research purposes on a wider scale as well as for personal asthma management. As well as more general desires *"to develop people's knowledge and education around asthma"*, participants also discussed contribution to large datasets. One suggested that,

> *"…for GPs it could be interesting to see if some of that data links into a spike in asthma and therefore they can readjust staffing to cope with extra footfall or for the hospitals…"* ***SIT026CM****, 42 yrs.*

6.4.6. Future applications of digital inhaler technology – desirability, ethics and wider impact

The responsible deployment of digital inhaler technology in routine practice requires wider considerations beyond efficacy. The collection of data as proposed potentially allows for a clearer, more accurate picture of an individuals' asthma and, consequently, for more targeted treatment. However, there are also ethical implications. For some participants, these were obvious – even volunteered. For other participants, these were less thought-through or less uncomfortable. This theme

explores both reactions and the specific questions that provoked them.

Desirability of the Smartinhaler™ system

Overall, participants were generally open to having a Smartinhaler™ in the future. For some, this was a matter of personality. They were self-confessed technophiles who were engaged by the prospect of being able to digitise and data-transform their asthma. Some participants felt that they would want to know that the devices would be more reliable first.

For others, desirability was largely dependent on cost. Participants generally felt the current cost of £99 per unit was expensive. Only a few participants thought this was acceptable, or even expected. For many, the price was off-putting and appeared disproportionate to the technology available. For a few, the high cost was justified by the potential for impact.

For most participants, the potential for impact (whether on their patterns of inhaler use or on their ability to take better control of their own asthma) was the main reason they would or would not want a device going forwards. This was the case whether they were looking at the potential for impact having experienced impact during the study or whether they were

anticipating this from the data that they expected would be generated.

> *"I think it just comes back to data, the more data you've got, the better you can understand and manage things so I'm all for it really."*
>
> ***SIT024CF**, 39 yrs.*

The subject of data ethics

Participants had both varying opinions and varying strengths of opinion on issues such as what data it would be acceptable to collect, where such data should be stored, how it should be kept secure and who should have access to it. Generally, these views ranged from ambivalence or conditional acceptance of non-healthcare interaction to more vehement distaste regarding the potential for non-healthcare entity interaction with their data. Each of collection, storage, security and access are explored in further detail below.

Data capture

The general feeling from participants was that we now live in an age of extensive data collection and so extra data collection was neither a new nor an unnerving concept. Furthermore, as

data collection would be aimed at directly benefitting their health, the purpose was largely seen to justify collection.

> *"… I think generally, anything to do with your health and wellbeing, if a process is trying to help you with that, then you need to be as open and as candid as you can, obviously if it's relevant."* ***SIT030IM****, 49 yrs.*

Some participants, as already discussed, maintained concerns around location data. Another suggested that a line would be crossed if there were camera or microphone capabilities added to such a platform. Also as already discussed, the idea of covert monitoring generated a strong reaction. With all forms of data collection, there seemed to be two issues at stake: a question of necessity and, perhaps even more key, a question of trust.

Data storage

Several participants were happy for data to continue being stored on manufacturers' servers on the condition that manufacturers only permitted access to relevant parties or that data remained anonymised. Several participants felt that a guarantee of data security, or NHS oversight, was required for this to be acceptable. Other participants were more hesitant,

primarily with concerns around data security but also in terms of data integrity.

> *"New Zealand is a bit too far, anything could happen., anything could happen to the reading…"* ***SIT006CF****, 27 yrs.*

Most participants, however, were clear that, should this sort of technology be employed as part of routine clinical practice, the data would need to be stored within NHS information technology systems.

> *"I think it needs to be moving into the NHS because if this is to have a positive direct impact on patients, what use is it sat with a manufacturer? That's okay for developing the products, the technology but that needs to be a two-way conversation, I think the data needs to sit with healthcare…"* ***SIT003IF****, 47 yrs.*

From a data security standpoint, there was a sense that there was greater accountability, where the NHS's primary duty being for the benefit of the patient/user. Some participants began to look beyond data security to how this would allow for better

continuity of care by linking in with other existing health records.

> *"I think it should be more on like individuals' medical records really, somehow synced to each person, I know it would probably take a lot, but everybody's different so it's unique to them, so if there was a way of doing it that way I think that would be better."* ***SIT009IF****, 34 yrs.*

Data security

On the whole, participants who discussed data security as an issue felt it was important. For many, anonymisation was key (with few exceptions). Others noted (particularly in light of recent media items) the importance of reassurance that servers were secured against breaches and that personal information could not be leaked.

> *"…that's the only big worry for me, is making sure that my personal information isn't getting into the hands of the wrong people and people who are going to hassle me on a daily basis…"*
>
> ***SIT005IF****, 27 yrs.*

One participant, however, uniquely expressed a lack of concern.

> *"I can't think of anyone that I'd be worried about because if they can get my data through one app, they can get it through another app so unless you block all permissions, people are going to find you if they look hard enough. I'm not worried about people hacking into my phone and taking my bank details, good luck to them..."* ***SIT015CM****, 41 yrs.*

Data access

There were mixed opinions on who should or should not have access to data. Some participants felt that access for profit was unacceptable.

> *"I think if they're going to make them rich, somebody you can't trust, I'm not against rich people but do you understand what I mean?! … I'm doing this study so that things can get better, not for companies to make millions of pounds, if you see what I mean."* ***SIT002CM****, 57 yrs.*

Others felt that access should only be provided to entities within the NHS, with some specifically naming pharmaceutical companies, health insurance companies and government as

bodies which should not have access to such data. However, for others, there was less discomfort about access being given to entities outside of the NHS. Indeed, for some participants, such access was important. One participant noted an advantage to manufacturers having potential access to data for ongoing product improvement.

> *"The people who are developing it to share amongst the healthcare professionals, I think are the most important people."* ***SIT014CF****, 57 yrs.*

Even here, however, several participants felt such access was dependent on their data being anonymised and access to patients and their healthcare teams being guaranteed. Participants not only felt that this should be available, but also that healthcare teams had a responsibility to empower users to understand their data.

> *"So, the fact that we're doing recordings and there's lots of data, if that's not user friendly … if there is medical data that, as a patient, I might not necessarily understand then just a bit more clarity around what, as a clinician, that suggests to you…"* ***SIT030IM****, 49 yrs.*

Participants also discussed how integration with health records could also lead to integration across primary and secondary care services so that this data would also be accessible to hospital specialists when they were referred for escalation of care.

What also clearly emerged from a group of participants was a sense that access, whoever it was given to (i.e. whether NHS or non-NHS bodies), should be on a need-to-know basis. The end-user's benefit should be prioritised. This may be directly in terms of the individual patient, or more broadly in terms of developing the best possible product for people with asthma.

Finally, some participants expressed their overall feelings in terms of trust, similar to views regarding data capture. In a similar vein also to discussions which took place around the acceptability of covert monitoring, there was a sense that participants would want to be given all the relevant information as to which parties had access to their data and what they would be using it for. They would also want the right to opt out if they wished and they would want to know that they could trust those.

"I suppose it doesn't matter who has access, so long as you're clear to whoever you're capturing

that data from, that that's where it's going, I think that's actually more important than who should or shouldn't, I think so long as you're informed and you have that choice as to whether you want that particular company or person to have access to that data, that's probably more important." ***SIT026CM****, 42 yrs.*

Participants' views on the potential wider impact of digital inhaler technology

Impact was generally interpreted at a personal level. A few participants, however, did also consider the wider potential for impact in people who had asthma.

"If that's the way that the future is going, then it's a way of monitoring more effectively, getting the information, reviewing it, to try and improve, the way we study asthma and the way that we treat asthma then I'm okay for that to be forever, if that's the way that it is."

SIT035CM*, 38 yrs.*

In terms of relationships with health providers, most felt it would have a positive impact by allowing care providers to respond rapidly in a more informed way. Objective data

provision, participants felt, would increase trust between GPs and their patients. Participants also felt that it would open up conversations, allow for better-targeted consultations which were backed up by a better picture of what was actually happening rather than relying or patients' subjective memories.

Not all participants felt so positively. Some articulated concerns that such data might lead to a power dynamic where patients feel "told off" by their GPs. Others worried about depersonalisation.

> *"…the risk is that they could just use the data and not … see how the patient was face to face, that would be a risk but then that probably depends on both the patient and the practitioner so … there's always a risk of becoming slightly more anonymous as a patient I guess, if there's more, if someone relies more on just data."*
>
> ***SIT001IF**, 54 yrs.*

Participants highlighted the importance of healthcare providers maintaining a two-way conversation with their patients that explored their feelings and worked around issues rather than automated responses to data.

On healthcare resources, a few participants recognised this sort of technology as having a potential for impact but were split over whether this would be positive or negative. On the basis of the current cost of the devices, some participants noted how challenging it could prove for the NHS to provide such a service. For other participants, however, there was a potential for benefit by reducing GP appointments, hospital appointments, unnecessary treatment escalations and emergency department and hospital admissions. One participant did note that such *"efficacy"* would need to be evidenced.

One participant linked the technology to public health messaging recommending greater self-management practices in the management of chronic conditions and the push towards increasingly personalised medicine.

> *"Even part of this is you're monitoring an individual, you're not making assumptions based on a population … I think that's the way it's going and I'm all for personalised medicine because what will work for you will not work for me but I think we're a bit away from that at the moment."* ***SIT003IF****, 47 yrs.*

For some participants, the impact – either experienced or potential – was great enough for them to foresee its potential for the wider asthma community. Most participants described themselves as already adherent but felt that it would be advantageous for people with asthma to have access to their own data.

> *"I could see it just being really useful long term and I think everybody should have a device and everybody should be able to see their information…"* ***SIT008CF****, 44 yrs.*

6.5. Discussion

6.5.1. Summary of study findings

At the final visit of a pilot study using EMDs as part of an adherence intervention, study participants discussed their experiences with the Smartinhaler™, how these experiences were in the context of their experiences with asthma and asthma treatment and how those experiences shaped their perceptions of digital inhaler technology as well as its potential for future use in routine clinical practice. Participants described how they contextualised their asthma from the (at times) belief-altering perspective of their recent experience of exacerbation, which was both an *"eye opener"* and a motivator to

maintain/regain control. They explained that they generally felt in control of and responsible for their asthma, and that healthcare teams could be contributors to this. For them, symptom control was generally defined in terms of a reliance on reliever inhalers or symptoms which led to frustration and limitation.

Similarly, they described how their perception of inhaler efficacy was tied to their previous experiences, whether a reduction in interval symptoms and increase in peak flow or a perceived increase in symptom burden despite reported ongoing inhaler use. Necessity was based on past experiences, generally of what had happened or (fear/lack of fear with regards to what could happen) in the absence of preventer medication. Participants also described the reassurance supplied by the presence of their reliever inhaler and discomfort with reliance on treatment. They described frustration where they perceived changes to their medication to be arbitrary. Participants described their patterns of inhaler use and the factors that affected those patterns, particularly highlighting the power of habit formation and routine in addition to the role of past experiences. They also described perceived unwanted attention from public inhaler use and a desire to keep their condition hidden.

Participants generally found the Smartinhalers™ acceptable, although for some this was a balance between issues such as their physical characteristics. They were largely in agreement that they preferred their EMDs to be subtle and non-intrusive (whatever their opinion of the size of the Smartinhaler™ device). There was some frustration around technical issues such as connectivity and data reliability. They placed a high value on ease of use (simplicity, in-app guidance, ease of replacement, ease of charging). Intervention participants variably found the in-app feedback helpful. Many participants described some level of impact, whether this was increased awareness of their condition, its importance, their ongoing symptom status or behaviours. This was sometimes dependent on baseline factors such as pre-study adherence and perceived drug efficacy. A few participants described engagement with clinical teams and varying responses from cynicism to interest and changes in management.

Participants generally felt desirability of a Smartinhaler™ system would be dependent on its potential for impact and had ideas for improving its physical characteristics, additional app features (without doing away with its simplicity), integrated data collection of environmental factors, physiological markers

(both automated from other mHealth systems and user-determined) and uses including enhanced self-monitoring.

They were mostly unconcerned about data sharing so long as it was on a need-to-know basis, for user benefit and anonymised/secure. Most participants were open to additional data sharing, fewer were open to integration with other systems including wearables and fewer (albeit still the majority of participants) were open to the use of GPS tracking. Some participants were more vociferous in voicing their discomfort with proposals, others more subtle – potentially projecting their discomfort onto "some/other people". Participants could see ways in which Smartinhaler™ technology could enhance their asthma care, but not many were happy for it to replace face-to-face conversations altogether. Participants felt that feedback should be in partnership with users rather than done to users by healthcare professionals as they wanted to be empowered to understand their condition. They saw this technology slotting into primary care due to relationships they had already built with primary care providers and their role in management. They felt that EMDs should be issued for long enough to gather a holistic picture of the user's asthma. They were generally optimistic that, particularly where data are used as stated, that this would improve communication with their clinicians.

Participants foresaw both positive and negative implications (usually in terms of cost) for wider impact.

6.5.2. Contextualising this study

Previous work

This study provides important insight into user perspectives from the point of view of an interventional study of adherence, a view only obtained by one other study thus far (184) despite some 30 years of adherence research (152). Unique to this study, however, is its understanding of how "control group" users in the context of non-covert monitoring interacted with their devices. This is key in understanding the effect a hands-off approach to EMD use may have in the clinical setting. Also novel is the presence of user (rather than clinician/researcher) perspectives on how such devices may be deployed in the future.

This study carries echoes of what has been seen before. As in the study from Stewart et al., participants were highly motivated to avoid experiencing repeat exacerbation or symptom deterioration (186). Participants were often optimistic about the role of healthcare professionals and potential role for EMDs in aiding in this endeavour. There was a high level of EMD desirability as found by Howard et al. (185) and, as noted by Foster et al. (184), this often persisted in the face of technical

malfunction. Some found the EMDs contributed to their ability to self-monitor and thus take ownership over their asthma. Some also found that it facilitated conversations around their medication regime in a similar way to that anticipated by participants in the study by Howard et al. (185) and discussed by participants in the study by Foster et al. (184). Also similar to the study by Foster et al. (184), participants found the EMDs to be effective reminders for inhaler use, even where the reminder alarms had not been activated and discussed how it had improved their preventer use, helped maintain routines, and changed their attitude towards various self-management behaviours. This supports its highlighting of the importance of habit formation.

As found by all three papers, however, these benefits were not universal. There were varying levels of acceptability of the devices' appearance and their potential to attract unwanted attention and therefore decrease inhaler use; although in this study, this was more around reliever use. Participants also drew links between baseline medication use, perceptions about medications, perceptions about asthma and EMD impact. Participants expressed concerns about data sharing and about the risk of depersonalisation in the face of their own data.

The in-depth interviews from the current study, however, go further, exploring participants' beliefs about both their asthma and their medication in greater depth. This is key. Farnesi et al. note that, "*…even when well-intentioned, attempts to persuade patients to adhere to biomedical treatments may prove futile if they fail to fit with the patient's beliefs, expectations, and needs"* (207). As Foster et al. noted, there were some beliefs that EMD provision only altered if it led to direct conversation with patients' clinical team (184). It would therefore stand to reason that participants with poor adherence behaviours prior to the study who perceive greater impact do so because they already have beliefs which are congruous with increased adherence and an understanding of the role EMDs play in enhancing these may provide a mechanism of action.

The sample in the other adult qualitative study, whilst being individuals with uncontrolled asthma, were not necessarily individuals with recent or frequent exacerbations. The current study, therefore sheds greater light on the strength of motivation the desire to avoid recurrence of negative asthma experiences provides to an intervention. It provides greater detail over precisely what individuals wished to avoid (activity limitation as well as, reliance on acute reliever medication use and unanticipated service use (186)). It also highlights that

participants are not only concerned about adverse effects from their inhalers. Beliefs of non-efficacy appeared to be important demotivation in a few participants that would require separate targeting.

Participants expressing such beliefs also reported periods of not engaging with this study. This is in keeping with findings from other adherence studies where, despite EMDs resulting in overall increased adherence, a subset of patients showed either persistent poor adherence or disengagement including reported device loss and damage (69, 99, 112). This group of individuals (high baseline risk, self-confessed poor disease control and beliefs which both work to demotivate adherence and prove resistant to simple interventions) is at increased risk of poor outcomes (12). Unfortunately, they are also at risk of being excluded from the evidence for inhaler technology adherence interventions by virtue of being more likely to disengage from studies and more resistant to interventions. Interestingly, a recent observational study of fractional exhaled nitric oxide F_ENO suppression excluded patients who were shown not to be adherent during a one week run-in period (112). Already, EMD-based interventions as they stand do not work for this group, as demonstrated by the studies above.

Whilst not by any means over-simplifying the complexity of these individuals (some of whom have refractory disease which plays into their poor adherence (99) and others of whom may have complex concomitant psychosocial circumstances or comorbidities) participants themselves suggest potential avenues of engaging with regular preventer inhaler use and doing so via inhaler technology. Thus, even though inhaler technology alone cannot answer these complex problems (184), it may be part of a multifaceted, holistic solution.

Informing application of behavioural change models in asthma adherence

Elements of all behaviour-change perspectives are relevant to EMD interventions. They are engaged in behaviour change on the basis that ICS has been evidenced to improve asthma control (biomedical), use social learning to establish and maintain new behaviours, can be used to acknowledge the rationality of beliefs undergirding poor adherence by providing evidence at an individual level of the benefit of regular ICS adherence, providing new experiences to alter old cognitive representations as demonstrated by Foster et al. (184), and facilitate communication with clinical teams. Current research on who they should be deployed in suggests that, for impact, users require a certain level of motivation – potentially, as

demonstrated in this study, recent exacerbation or experience of deteriorating control leading to functional limitation, increased medication requirements or unscheduled service use.

Participants' emphasis of beliefs, perceptions and, in particular, the memories of the experiences and emotions that shaped them appear to support the validity of a self-regulatory model for behaviour change in asthma, even beyond Horne's *necessity-concerns* framework (59). The data also suggest that harnessing these experiences and emotions at a personal level may be a significantly powerful motivator for change. Some of those beliefs are well-elucidated in the health belief model, particularly *susceptibility* and *seriousness*. Importantly, however, in describing factors which led to them adhering to their medication as prescribed, participants emphasised routine and habit formation, a finding echoed by Foster et al. (184), an element more in keeping with a social learning perspective but which may also fit well into the action-planning part of the self-regulatory model. Such paradigmatic integration is in line with Leventhal's own aims in promoting a self-regulatory framework (190). Whilst self-efficacy was less directly emphasised, participants' clarity on their sense of responsibility for and control over their condition (and, where control) was absent, their desire to regain control suggests that individuals with

asthma do want to feel empowered to control their own disease. As Stewart et al. demonstrate, there is a risk that EMDs can work contrary to this (186). There is therefore likely to be benefit in considering the theoretical basis of how they are deployed so that this is not the case.

Future applications for inhaler technology

This is believed to be the first study that has explored in depth the unique and expert perspective of individuals who have experienced EMD as an intervention to improve adherence in asthma in understanding how proposed future uses of EMDs interventions and ethical issues related to this were received. Other studies have explored such themes in less depth (185, 186), with individuals who have not used EMDs as an intervention and therefore lack the expertise of experience in this area (208) or more narrowly in relation to EMDs as they exist in their current form and use (184).

The current study went beyond desirability to understanding potential for impact as based on participants' own experience, both with a basic app and an app with in-app data and associated feedback. It also examined where it would fit into services, how such uses would be perceived by the individuals who could be affected by them, what platform integration could look like and how useful individuals with asthma actually

perceive this to be. This is particularly timely in the light of NHS England's requirement for adherence to be evidenced objectively before treatment escalation to biological therapy (34) and the anecdotal increasing use of EMDs in that process. It is also timely as work is already apace testing integration of EMDs with other mHealth inputs, including several suggested by participants in this study (209, 210).

Also timely is this study's sounding of participant views on data ethics, particularly in light of recent controversies (211). As interest in mHealth rises, so important questions need to be answered. Who safeguards the interventions and their effects on individuals, whether this is in the form of information and its evidence base (212, 213), the human factors effects which may be yet unknown (214) or data security and confidentiality (215) as highlighted by the DeepMind controversy (211)? On a wider scale, what effects will such technologies have on health equity, on health infrastructures and on the boundaries between commodification and the human right to health (214, 215)? In the qualitative tradition, this study pushes to the fore the voices of the individuals for whom these issues will have the greatest relevance. By acknowledging the centrality of the patient role in their own self-management, it utilises these user perceptions

and experiences to inform potential implications for EMD interventions as part of future clinical care.

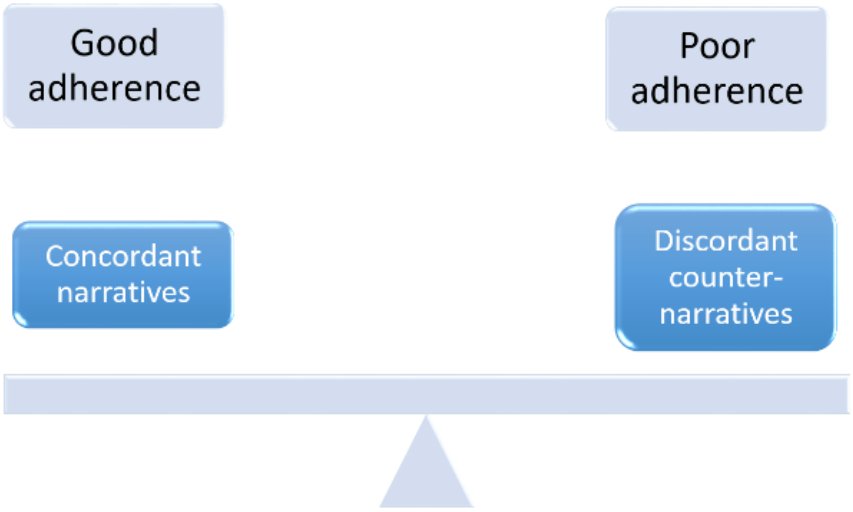
6.5.3. Applying this work to future intervention practice

Unsurprisingly for such a heterogeneous condition, this study demonstrates significant heterogeneity of baseline experiences and beliefs. Individuals who entered the study used these experiences and beliefs to construct stories which helped them make sense of their asthma and its treatment. These stories seemed to motivate (or demotivate) habit formation which led to adherent or poorly-adherent inhaler use behaviours. Using a self-regulatory framework, the aim of EMD interventions is twofold. As a simple intervention, they can assist individuals who have stories consistent with adherence behaviours which increase their asthma control and decrease their asthma risk (equivalent to Leventhal's *cognitive representations* (190)) to take actions in line with those beliefs. The primary action identified by this study is habit formation. The second aim is to, where needed, work with individuals to modify stories which do not motivate behaviours that lead to increased asthma control and decreased asthma risk. Discussed below is a framework to practice approach drawn from this interpretation of the data.

Targetable beliefs and story modification

The data presented in this study suggest that, within the stories that individuals have constructed about their condition from their perceptions, experiences and emotions – whether its aetiology, their symptoms, its effect on them or their medications – lie key targetable beliefs. Thus, overarching stories may not be fully concordant or fully discordant with adherent behaviour. Rather, they may demonstrate a balance of adherence-concordant beliefs set on a scale against adherence-discordant beliefs. Resultant behaviour would depend, as it appeared to from our data, on which beliefs weighed more heavily. Similarly, Scherman and Löwhagen found that medication behaviours depended on which belief-forming experiences achieved dominance (216), as illustrated by *Figure 6-2*.

Figure 6-2: Stories are constructed from a balance of concordant-discordant beliefs



Individuals' perceptions and beliefs around both their asthma and its treatment have consistently been shown to interact with their self-management behaviours (trigger avoidance, lifestyle and adherence) (183). Evidence also suggests that self-management behaviours will be most effectively influenced when clinicians take the time to engage with beliefs, inviting their patients into *"a shared understanding of how the disease manifests itself in a specific patient"* (207), rather than simply dictating the terms of reference (183, 207). This was just as much the case where discordant habits were leading to harm, as individuals did not always automatically relate their symptoms and limitation to poor symptom control or self-management behaviours (207).

Examples of key targetable discordant beliefs from this study include:

- The belief that asthma is not a serious condition. Studies have shown that the understanding of asthma as a serious condition is fundamental for participant engagement in their intervention (184) and associated with higher levels of concordant treatment necessity beliefs (182).
- An individual's belief that they are not themselves susceptible to serious asthma. In this study, this belief was targeted by the use of asthma control and quality of life questionnaires and the awareness of their reliever use resulting from knowing their inhaler use was being monitored. This was reported by both intervention and control participants. In one study, participants recalled their objective data challenging previously-held perceptions of their own adherence, again, helping them to understand their susceptibility (184), likely to in a similar way to which participants in this study described their EMD as helping them to be *more* regular users.
- The belief that preventer inhaler use is unrelated to asthma symptoms. Foster et al. demonstrated how EMD provision led to experiences which helped users to link

their regular preventer use with improved asthma control (184).

- The belief that inhaler use is embarrassing and results in unwarranted attention. Some studies show an association between such feelings (the fear of increased attention stemming from their asthma, embarrassment, unease with public inhaler use) and lower levels of adherence (182). Whilst in our study response was mixed, for some participants the novelty of the inhalers gave them confidence to engage with them in public in a way in which they previously had not.
- The belief that overuse of their reliever is necessary. A couple of participants in this study attempted reduction of excessive reliever use in response to seeing their data showing that the process had challenged their beliefs around how often they truly needed their reliever inhaler.

For some individuals, simple provision of an EMD-based intervention will be enough to tip the scale in favour of their more concordant beliefs. Those who do not respond can be stratified out and receive targeted intervention. This would ensure that no patient is left behind without leading to the expense of undeliverable, complex interventions targeted at people who do not need them.

Habit formation and adherence behaviours

Most individuals in this study reported themselves (some confidently, some less confidently) as using their preventer inhaler religiously or regularly with occasional missed doses or overuse. This suggested a belief, at least, that preventer inhalers *should* be used regularly, even when participants (often apologetically) admitted that they were not. Participants were also keen to exert control over their condition and felt a sense of responsibility to do so. These participants also discussed partnering with their clinical teams to achieve personal agency over their condition. That these participants were not necessarily universally adherent would suggest that beliefs alone are not enough to influence behaviour. This prominence of habit formation is in line with the findings of Foster et al. in their qualitative study of experiences with EMDs (184).

Data from this study suggests key parts of habit-formation include:

- Visual cues (seeing their preventer on their bedside table or by their toothbrush for example)
- Auditory cues (reminder alarms, important others)
- Routine (e.g. timing preventer inhaler use with other key daily routines)

Data from this study also suggests that EMDs may stimulate habit formation through:

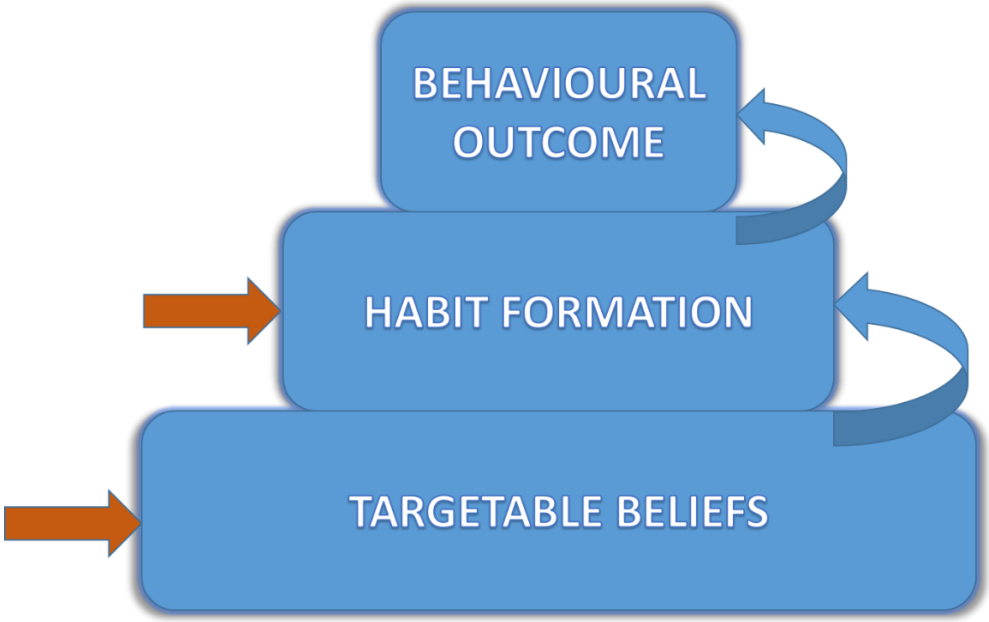
- The awareness of being monitored, emphasised by in-app feedback and device characteristics such as the LED flash at data upload and device novelty
- Reminder alarm function activation (auditory cue, reducing habit loss when there is a change of routine)
- The ability to check whether a dose has been missed (also reducing habit loss when there is a change of routine)

This may be enhanced by other forms of feedback to keep the user engaged.

Suggested model to inform practice

Based on both previous literature and work presented by this study, an integration of what is known into a working model is suggested (*Figure 6-3)*. This proposes that behavioural interventions work by targeting specific beliefs which are amenable to change as well as by stimulating habit formation in order to see the desired behavioural outcome.

Figure 6-3: Proposed Beliefs - Habits - Behaviours Model



For some individuals, beliefs may not need to be targeted directly – simple reminders leading to habit formation and reinforcing concordant beliefs may be enough. For others, without a more complex intervention to target beliefs, habit formation (and consequently, behaviour change) will not be attained. Even here, however, successful modification of beliefs will only lead to modification of behaviour if habit formation is reinforced as well.

6.5.4. The future of EMDs

It has been stated that, *"attempts aiming at enhancing asthma control should combine strategies targeting the individual diagnosed, the health care organisation, and community"* (207). In this study, EMDs were described as having a level of

impact in all three spheres. Perhaps most exciting was how participants saw the future of EMDs. Research in this field is still young and has almost exclusively focused on the impact of EMD technologies on asthma control through improving adherence. However, as Farnesi et al. noted, *"…patients viewed asthma management and control to provide more comprehensive assistance regarding behavioural changes to be implemented…"* (207). Participants in this study were similarly curious about the potential for an integrated inhaler technology platform to inform their lifestyle choices around exercise and safety in exercise, around trigger avoidance and increasing awareness of the risk that particulate air pollutants pose to people with airways disease as well as information on the weather and pollen. More practically, they wanted an opportunity to be able to integrate this with their current status – symptoms, questionnaires and physiological markers – in order to both self-monitor and better inform their healthcare providers. This desire for better-informed, more personalised care and information has been noted to come from the desire individuals with asthma have to have a greater sense of control over their condition: i.e. *"knowledge is power"* (217).

Exploration of these future avenues may contribute to more than just patient engagement. With the growing interest both

within the asthma community (218, 219) and the public imagination (220) of air pollution, for example, it may be that these less studied features prove important in improving asthma control in the future. EMD technology may offer solutions to the resource strapping of recent years that has made time an increasingly unavailable commodity and affected continuity of care. By providing clinicians with tailored information, they allow for delivery of personalised care supported by personalised information which is validated and available to users at the touch of a button and takes into account their current status, environmental factors, physiological markers as well as inhaler use.

Finally, users are clear that they want data to enhance, not replace, interaction with healthcare teams. They are clear that they want their data to be secure, they want to be fully informed of what it is being used for and they want control over what they share and whom they share it with. Finally, they are clear that they expect integration between their primary and secondary care teams. This should be accounted for in service delivery.

6.5.5. Strengths and limitations

This study explores much-needed and previously neglected research into user perspectives on EMDs. It offers novel work,

particularly in terms of future use of EMDs. Participants were asked to hypothesize based on their experiences into potential implications in the future. The findings from this are important (and, to this investigator's knowledge, an equivalent has not been attempted before). This is a major strength of the study. Whilst acknowledging the nature of this part of the interview as extrapolative rather than based in experience, it is still superior as a source of information to the research and scientific community conducting such extrapolations on the behalf of their patients.

In addition to the transferability and novelty of its findings, strengths of this study included the duration of time participants were provided with an EMD. A six month duration allowed participants significant exposure to the EMD and reduced the novelty effect, such that experiences were perhaps more reflective than a shorter study of what effect such devices used in clinical practice would potentially have. This study also involved a sample that had significant experience of asthma morbidity, providing a rich source of information with regards to experiences of asthma. Finally, this study's use of behavioural change theory has further focused data into an implementable strategy for care.

This study shares the limitations of most studies in generalising findings. This is particularly the case from its qualitative nature as well as in terms of demographics – the study sample was overwhelmingly female and Caucasian, for example. Findings are therefore the perceptions and experiences of this unique group of individuals. However, they offer valuable and novel insights and perspectives that can inform not only future digital inhaler interventions but also inform clinician approach to their patients. This is strengthened by the fact many of the base findings are supported by research in this field. Whilst these findings cannot be generalised *per* se, the themes drawn out and the model developed are transferable to other asthma populations.

Some of the experiences participants were asked about were from prior to study entry. It is inevitable that, for at least some participants, these experiences will have been modified by various aspects of participation in the study. However, this risk was balanced against the need to minimise emphasis on adherence at the start of the study. Such an emphasis may have resulted in a Hawthorne Effect (143) on behaviour by emphasising themes around medication and control. It is also noted that participants were also asked to discuss their experiences and perspectives immediately the study closed,

reducing the opportunity for them to have time to process and contextualise their experiences. As discussed in the methodology, however, the benefit of maintaining engagement and minimising memory bias was judged to outweigh this.

6.6. Conclusion: Incorporating patient experiences and perspectives into future technology delivery

Inhaler technology has shown promise in improving adherence but has less evidence in showing that this leads to improvement in clinical outcomes. This may be in part due to interventions which assume individuals with poor medication adherence are a homogenous group. There is also a risk that studies continue to exclude (or fail to show benefit in) individuals with complex underlying causes for their poor adherence who are potentially at high risk of poor outcomes.

This study proposes a targetable beliefs/habit formation model, which may help researchers and clinicians deploy inhaler technology in a way that is more effective in terms of clinical outcomes and that also benefits individuals with more complex needs. It further proposes a willingness for a more integrated, platform-based approach which may help clinicians target not only adherence but various elements of overall asthma care.

This study also suggests a general optimism from individuals with asthma for the potential of inhaler technology to have both personal and wider impact. There are, however, rules of engagement, particularly related to usability, reliability, data security and data access. Manufacturers, researchers and service providers would do well to pay attention to these if EMDs are to have the impact they are capable of.

Chapter 7: Inhaler technology: translating from clinical trials to routine use

7.1. Findings of the thesis

This thesis set out to investigate the effectiveness of electronic monitoring devices (EMDs) in the monitoring of adherence and delivery of interventions. It also set out to understand the implications of this for their routine clinical use.

A meta-analysis of studies using EMD-derived adherence found that electronically monitored individuals with asthma actuated 64.3% (95% CI 57.1-71.5%) of puffs prescribed. This estimate is higher than that found in previous reviews incorporating various methods of adherence monitoring (46, 50), likely reflecting selection bias and observation effect (see *Chapter 2*). The review also found that interventional studies saw an improvement in adherence (i.e. proportion of prescribed doses actuated) of 12.7% (95% CI 6.1 – 19.3%), suggesting that EMDs are a good measure of change in adherence. However, there were also a wide variety adherence definitions. What devices actually measured and how this was reported differed across sample populations. This review also found differences

between technological features of different devices and device accuracy. These were all judged to be factors which could affect development of effective interventions and, ultimately, EMD use in clinical practice.

In its second review, this thesis also confirmed that EMD-based interventions improved adherence. However, it found that the gains in adherence did not consistently translate into improvement in clinical outcomes. This was despite established evidence that good adherence to inhaled corticosteroid (ICS) results in better clinical outcomes (31, 32).

As part of a pilot study of an EMD-based intervention, 130 devices were tested. As 12% of devices failed both in pre-study and post-study testing, this thesis concluded that quality control remained a barrier to widespread clinical uptake. The causes of the device failures largely related to the device casing-inhaler fit.

The thesis centred on a pilot study isolating feedback as an EMD-based adherence intervention. It found that the intervention group actuated 11% more of their prescribed inhaled corticosteroid (ICS) doses, although this was not statistically significant ($p=0.319$). It also found a difference in the proportion of individuals who took their ICS inhaler on

average ≥75% of the time. This approached significance (p=0.056). A follow-up power calculation suggested that a sample of 340 would be required to see a statistically significant difference in adherence between groups. This may indicate that the effect of feedback alone may not be enough to justify the use of EMDs in clinical practice.

There was no evidence of improvement in clinical outcomes but there was a trend towards an increase in exacerbation rate in the intervention group (p=0.069), suggesting that the relationship between adherence and outcomes may not be as simple as previously thought. Finally, adherence in the control group changed over time, suggesting that there may have been an observation (Hawthorne) effect i.e. the control group's adherence was increased by imminent past and imminent future face-to-face study visits.

Finally, user experiences of participating in an EMD-based intervention, their perspectives on EMDs and their perspectives on potential future uses of EMDs were investigated. Findings from this qualitative study demonstrated that, while users were open to a role for EMDs in asthma care, this was not unconditional. They wanted to see evidence of impact. For some, this would involve greater reliability, for others integration with other avenues of data and clinical care. Users

were generally clear that they expected their data to be anonymised and secure, that they expected access to their data and that they expected to be empowered to understand their data. They expected their data to form a part of (but not replace) clinical reviews. Participants valued a sense of control over their condition. They saw a role for EMDs in helping with this including by supporting their adherence behaviours and giving them access to reliever data to help them monitor their symptoms. They also thought positively about potential future platform integration (e.g. with wearable health devices).

7.2. An ideal study: from pilot to real-world

A key aim from the pilot study was to investigate feasibility of a fully-powered randomised controlled trial (RCT). Both the systematic review of electronically monitored adherence and the review of EMD-based adherence intervention further highlighted important study design considerations that should be incorporated into future interventional EMD studies. Based on the findings of this thesis, proposals for the ideal interventional study are detailed below.

7.2.1. Target population of an ideal EMD-based interventional study

Only two studies have shown a clear improvement in clinical outcomes from the use of an EMD-based intervention. These were both in children who had recently exacerbated (69, 71).

Questionnaire-defined asthma control alone was insufficient in highlighting the at-risk populations most likely to benefit from adherence intervention (*Table 3-4*). Thus an ideal study would enrich for poor asthma control as measured by recent exacerbation, ideally within the three months preceding the study.

Both of the reviews in this thesis found that baseline adherence had not been routinely reported. Where it was reported, it had been measured in different ways. The pilot study noted that a high baseline adherence may have masked any adherence gains or, perhaps more importantly, made a threshold improvement in clinical outcomes unattainable. Adherence interventions, by definition, are best targeted at individuals with poor baseline adherence. Identifying these individuals and retaining them in a study is likely to be challenging, however future studies of adherence must find ways of identifying individuals at risk of poor adherence and enriching for it. In its systematic review, this thesis challenges the idea of a run-in period as an effective measurement of baseline adherence. Measurement using pharmacy records and/or adherence questionnaires may help identify individuals who are more likely to benefit from adherence intervention instead.

Whilst there is no consistent evidence for the independent role of socioeconomic status in adherence, studies suggest that it cannot be ignored (53, 100, 118). Similar to socioeconomic status (221), certain ethnic minorities are known to have poorer asthma outcomes (222-227). Potential mechanisms for both socioeconomic status and ethnicity include out of pocket costs of medicines (228, 229), low health literacy impacting beliefs and behaviours (230) and beliefs about health and medicines (56, 60). Despite this, many studies have been shown by this thesis not to report socioeconomic status or ethnicity. Where reported, studies – including the pilot study presented here – with a small ethnic minority proportion have been unable to address barriers unique to this at-risk population. An ideal study would identify these at-risk populations and analyse data such that effective interventions can be tailored to their needs.

It may be that individuals with evidence of airway inflammation may benefit more substantially from improved adherence than individuals with poor adherence and no evidence of current airways inflammation. An ideal study would therefore include a subgroup of these individuals to aid future understanding.

7.2.2. Sample size for an ideal EMD-based interventional study

Chapter 3 describes how previous studies of EMD-based interventions have used sample sizes of anything between 20

and 330 participants to power for an adherence effect size of 10-15% for a variety of interventions in more than one demographic. The pilot study presented in this thesis suggests the need for a larger sample size. In it, the intervention group had an overall mean study adherence of 70.7% and the control group a mean adherence of 59.4%. Using this effect size of 11.3%, a sample size of 340 would be required (alpha <0.05, power = 0.9) for the difference in adherence to be significant (*see Chapter 5*). A loss to follow-up rate of 17% suggests over-recruitment allowing up to 20% loss to follow-up could be needed.

Power calculations for clinical outcomes were less commonly reported by interventional studies reviewed by this thesis. Where they were reported, sample sizes varied between 76 participants for a 0.5 point difference in ACQ and 188 participants for a 1.5 point difference in in ACT™. No published EMD-based adherence intervention studies have been powered on exacerbation reduction as yet. In children, a significant reduction in exacerbations was seen in a sample size of 89 and in adults, an unadjusted signal was seen in a sample size of 129. These were both for EMD-based adherence reminder interventions.

Drawing both adherence and clinical outcomes together, an overall sample size of 425 participants is suggested (340 with over-recruitment to account for a 20% attrition rate). This would be larger than any EMD-based interventional studies to date, positioning it to be powered for both adherence and exacerbation reduction.

7.2.3. Interventional arm of an ideal EMD-based study

The main brands of EMD device now in use collect date and time stamps and this should continue to be the minimum requirement. There is no evidence for devices collecting more information (i.e. presence of inhalation, quality of technique) and no device on the market currently has the ability to provide biological feedback in the mode of real time continuous glucose monitoring (rtCGM) systems. Nevertheless, it stands to reason that such devices may, by engaging users in their own care and reducing alert fatigue, have a greater impact than devices measuring date and time stamps alone and not providing feedback directly to users.

This thesis suggests that device accuracy is more important both to device users than and for study integrity than what devices are capable of doing (see *Chapter 4, Chapter 6*). An ideal study would prioritise devices with validation data showing good accuracy and allocate time and resources to device testing

before, during and after usage. An ideal study also needs to maintain clear avenues of communication between the study team, device manufacturers and inhaler manufacturers in order to allow emerging issues in device design or accuracy to be addressed during the course of the study. At least one member of the study team should have had experience using such devices, either in the context of research or clinically to minimise time lost in the testing phase due to lack of familiarity.

Whilst the pilot study suggests the possibility that feedback alone may be less effective than other methods of intervention, this thesis notes that studies combining reminders with feedback have tended to see their intervention group maintain a higher level of adherence. In contrast, studies using reminders only have tended to see a decline in adherence in their intervention groups. Whilst a large study of adherence as described above would be powered for feedback alone (with an expected effect size of 11%), combining feedback with automated reminders is likely to increase intervention impact and, consequently, effectiveness. A potentially greater distinction between control and intervention groups than that observed in the pilot study would increase the possibility that a difference in clinical outcomes between the groups may be observed.

In planning a study intervention, the ideal study would propose a mechanism for identifying participants who do not respond to the EMD-based intervention. It would then have a standardised way of assessing for common beliefs based on current evidence which are preventing formation of adherence habits and target them. Interventions to address such beliefs are likely to be more complex and not required in all participants. As incorporating them into an ideal study is likely to be challenging, the characteristics of participants identified as standing to benefit from more complex interventions could be collated and described to support future work in the area.

Participants discussed the desire to see EMD-based interventions link in with data which gives them a sense of control over their asthma, such as trigger data. Incorporating such data is likely to maintain study engagement and may also provide initial data in this area. Much of these data can be provided using already-available apps in smartphones.

7.2.4. Control arm of an ideal EMD-based study

EMD-based adherence studies are difficult to control, particularly where monitoring is not covert. Whilst this thesis suggests blinding may not be essential to show EMD impact on adherence, it also suggests that inherent study biases such as a lack of blinding may lessen an intervention's effect size by

increasing control group adherence. Furthermore, a Hawthorne effect may lead to EMD provision and study visits having an impact on some participants. Again, any resultant increase in control group adherence from this could lead to a reduced intervention effect size.

Separately, because in an EMD-based intervention, the EMD is also the mode of measurement, lack of engagement may also lead to loss of study data. In the pilot study, five of the six participants lost to follow-up belonged to the control arm of the study. It may be that participants who are at higher risk of disengaging from the study process are also at higher risk of disengaging from health services and self-management practices. Loss of engagement of participants who are more likely to be poorly adherent could also lead to a reduced effect size.

In an ideal study, the control group would not receive any input beyond usual care from a medical or research team with the exception of EMD provision and outcome data collection. Data should be collected with as light a touch as possible. User perspectives presented in this study suggest a possibility that engagement may be maintained by using the EMD as a platform for integrating other mHealth data. Collection of non-relevant electronic data such as heart rate might encourage continued

use of the electronic device in participants who may otherwise have disengaged and whose data may have consequently been lost.

7.2.5. Outcome measurement in an ideal EMD-based interventional study

Adherence should be defined as the proportion of ICS doses prescribed which have been taken. This should have a dosing time separation of at least 6 hours and be capped at 100% per dosing period. Overuse should also be reported. Feedback to users should distinguish between doses taken after midnight and doses taken on waking. Dosing effectiveness (e.g. quality of technique) should be investigated as a secondary outcome as, whilst it is intuitive that this would be superior to date-time measurement only, there is as yet no evidence to confirm this.

This thesis has noted that, whilst an improvement in adherence of 13% is estimated across RCTs, effect sizes of this magnitude have not led to much significant change in clinical outcomes. Much of this ideal study design assumes that the issue has been poorly targeted, overly-heterogeneous sample selection and a lack of clarity of interventions. However it is also possible that the magnitude of effect size generally seen and powered for here is not large enough to see the sorts of improvements required. A subgroup analysis of individuals who do show a

response in adherence should therefore be assessed for translation of this response into clinical outcomes. Similarly, a subgroup analysis of individuals who have shown a response in clinical outcomes (if this occurs) should also be reviewed. These subgroups should be assessed for characteristics (e.g. degree of change in adherence, baseline asthma control and behavioural characteristics) which they might hold in common and might inform whom such an intervention should be targeted at in clinical practice.

In addition to adherence, an ideal study would be powered for asthma exacerbations. These should be measured in terms of clinical symptoms and systemic steroid use. Other markers of deteriorating control or airways inflammation such as peak flow/forced expiratory volume in one second (FEV_1), serum eosinophilia or fractional exhaled nitric oxide (F_ENO) may also be of use in quantifying the clinical response to improved adherence. F_ENO has already successfully been used to distinguish adherence from non-adherence (112). Subjective asthma control should be measured using derivatives of the Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT™).

7.3. Electronic monitoring technology beyond asthma

Electronic adherence monitoring has been identified as holding promise beyond asthma. One such area is hypertension, which bears similarity to asthma as a largely asymptomatic disease with significant consequences for poor control resulting from poor treatment adherence (231, 232). Early systematic review suggested potential value in EMD-based or EMD-supported interventions, particularly for individuals identified as having 'drug-resistant hypertension' (231). With only a few exceptions (233, 234), these studies were largely noted to be of short duration and low quality (231). Challenges which may bear significance in the asthma setting included the clinical relevance of observed changes in adherence (41, 233), the importance of targeting interventions at specific populations in order to see an improvement in adherence (235) and overcoming the Hawthorne effect (235, 236).

Another area which may be more indicative of the ultimate goal for these systems may be to develop an asthma equivalent to intermittently scanned continuous glucose monitoring (isCGM), also known as flash glucose monitoring. This system integrates sensor technology with mHealth to reduce the need for recurrent skin pricks compared to traditional blood glucose monitoring (237-239) reducing costs related to blood glucose

monitoring (240). It potentially reduces the risk of alarm fatigue compared to real-time continuous glucose monitoring (rtCGM) systems (239), as well as reducing periods of hypoglycaemia (237, 238) with their associated healthcare costs. All this whilst achieving a similar level of blood glucose control to blood glucose monitors (239).

These principles – integration of biomarker measurement with accessible interpretation leading to clinically impactful behaviour change – are not yet available in asthma, although some systems are approaching this (112). For EMDs, there remains a need to demonstrate to users the benefits of inhaler use and to communicate this in real-time in a way that effects behaviour change. A major challenge is that the benefits of ICS adherence occur over time and there are few specific biomarkers, other than peak flow, that are easily measurable outside of the clinical setting. Potential advances may include integration of environmental sensors to show more personalised benefit (209) or with other biomarkers such as F_ENO should its cost become less prohibitive in the future.

7.4. Implications for future research

This thesis highlights key challenges in study design including selection of individuals likely to benefit from intervention, measurement of baseline adherence, heterogeneity of

intervention and outcome measurement and issues with regards to EMD accuracy. It highlights the fact that these design challenges are not merely academic. Rather, they are likely to be important factors in the lack of consistent clinical outcomes data from studies in this field.

There is a risk that adherence studies continue to be designed with no attention to either historic design flaws or patient perspectives, resulting in more data which still lacks definitive evidence of clinical effect, particularly in adults. An ideal study is described, but even with many of the design flaws identified by this thesis addressed and more effective interventions incorporating real-time reminders, feedback and targeted behavioural change proposed, it is unlikely that such a study would immediately pave the way to widespread uptake in clinical practice. Careful considerations such as cost-benefit analyses, data management and device accuracy are required and are discussed further below.

Modern life is ever-increasingly connected, ever-increasingly digitised. This has been described as the 'internet of things', where not just computers and smart phones but home appliances, televisions and cars are part of this intangible network. There is a certain inevitability that this will extend to solutions in healthcare.

Technological development continues apace, outstripping the speed of traditional modes of evidence-gathering. Such a situation presents a real risk that a window of opportunity for employing health technologies, including digital inhaler technology, for actual patient benefit will subsequently be lost (152). Future research assessing the benefits of adherence technologies should therefore seek to incorporate as much as is feasible and practical from the considerations presented by this thesis with the aim of impacting clinical outcomes i.e. control and exacerbations.

Beyond this, this thesis presents a case for asking new questions and seeking new ways to answer them. As interviewed participants discussed the importance to them of maintaining a sense of power over their condition, the utility of increased awareness and the centrality of both beliefs and habits highlight not only potential mechanisms for improving adherence but also ways of engaging individuals in their own chronic disease management. It highlights the reality that, for a sizeable proportion of those individuals at greatest risk, a different approach to the one-size-fits-all interventions of the past is desperately needed in the same way that severe asthma management is now personalised and specific.

Studies until now have targeted adherence as upstream of outcomes but have rarely found ways to parse and measure outcomes which are upstream of adherence. Understanding this has been key to the success of digital monitoring in diabetes, where the outcome measure of interest became blood glucose monitoring frequency and measures of patient satisfaction, allowing their widespread real-world adoption and for clinical benefits such as reductions in HbA_1c and glycaemic emergencies to be observed (241-243).

In summary, this thesis suggests that, unless the appropriate population is engaged, appropriate interventions are used and, where required, more complex interventions are targeted according to an individual's behavioural 'phenotype' (including past experiences, underlying beliefs and current habits), EMD-based adherence studies are unlikely to see consistent improvements in clinical outcomes. New ways of assessing successful outcomes may also need to be employed if inhaler technologies in the long-term are to have any more usefulness than that of a digital gadget.

7.5. Implications for future use and for clinical practice

This thesis finds that there is currently inadequate evidence to suggest the use of EMD-based adherence interventions in clinical practice, particularly for adults. If the evidence for EMD-

based adherence interventions can be strengthened, however, it does suggest the cohort likely to benefit will be those with poor baseline adherence, recent exacerbation and non-adherence which is amenable to simple intervention. Of concern, however, there are individuals who have more complex behavioural needs and who have been highlighted to be at particular risk of poor outcomes (12). That some studies note a small group of individuals who, even when exposed to a successful intervention, appear resistant to change their behaviours suggests that these individuals may not respond to simple interventions (69, 99).

This thesis did not include a health economic analysis. EMDs used purely to increase adherence are expensive (6, 154). Interviews conducted in *Chapter 6* made it clear that not all consumers are willing to bear the brunt of the cost. Direct-to-consumer sales models may thus exacerbate already-existing socioeconomically-driven health inequalities in asthma, but without strong evidence to support healthcare-wide adoption, this may be the model for the foreseeable future. Financial costs are not the only costs to consider. Incorporation of these devices into normal inhaler devices carries an environmental cost, as highlighted by some interviewed participants. Privacy

is another potential cost which, if these technologies are not carefully implemented, risks being a significant concern.

The 21st Century has already demonstrated the dangers of assuming that the ethics of the digital space will evolve in a way that is beneficial to the individual. Whilst individuals may be happy to share much of their personal data in the current digital age, scandals such as the Facebook/Cambridge Analytica scandal and the Google DeepMind controversy demonstrate that general consent cannot be assumed and is not limitless. Healthcare data is sensitive and may place individuals in vulnerable position.

Participants in this thesis have indicated that trust is key and that the purpose for which data is to be used and the organisations which will have access to and oversight of their data are important considerations. Once these have been made clear and appropriate protective measures are in place, many have no objections to data use and sharing. However such good will must not be exploited and this important issue which faces society as a whole cannot be ignored by researchers, clinicians or other stakeholders in this field. Privacy and the ethics of digital health data is an area into which careful research and investment are urgently needed.

The question of adherence monitoring as the sole use for EMDs may itself become obsolete. Cheaper ways of encouraging increased cumulative ICS exposure in the context of poor adherence, such as use of ICS/LABA (long-acting beta agonist) as reliever in mild asthma (24, 97, 244) and increased ICS dose during exacerbations (6, 245) are already gaining traction. The future use of these devices may therefore rely on their ability to anticipate the future of the digital space in asthma. Beyond adherence, this could include devices which have the potential to be integrated into self-management education, disease monitoring and control as well as treatment escalation and response. These uses will require the employment of qualitative research findings, such as those presented in this thesis, in order to understand more clearly what patients with asthma and their clinicians want from technology. It will also require the presentation of data outputs in ways that are interpretable for users with asthma, as well as standardised and clinically useful for their clinicians.

Finally, these devices are only as useful as their data outputs are reliable. A major issue highlighted by this thesis was the significant failure rates of devices, both in *Chapter 2* which reviewed previous literature, and in *Chapter 4* where in-house validity testing was conducted. This is particularly an issue

where devices are employed to assist in treatment decisions. Clinicians in the real-world cannot be expected to conduct quality assurance processes. As the technology advances, it is expected that new models with greater capabilities will be produced. Ways of rapidly validating these models routinely and publishing such data are needed for their effective use in clinical practice.

7.6. Conclusion

Smartinhaler™-like technologies and platforms hold significant promise; however, this promise remains unfulfilled. Current data suggests that this may not simply be due to a true absence of clinical effect. Study design factors and factors which may mediate between adherence and clinical outcomes may also be responsible. Considerations for EMD translation into clinical practice include reliability, consistent demonstration of clinical effect and output of accessible, meaningful data for both users and clinicians.

Even more importantly, this thesis presents a pressing need to target interventions at individuals at greatest risk, who stand to benefit the most from using these technologies. As more simple interventions (such as maintenance and reliever therapy)

challenge the role of inhaler technology, the future may lie in its ability to integrate multiple platforms to engage the individuals for whom usual care is not preventing morbidity or mortality.

This thesis concludes that, as they stand, the evidence for using Smartinhaler™-like technologies in clinical practice to improve adherence is inadequate. It furthermore concludes that they should only be used as adherence measures where local quality control procedures are feasible.

References

1. GINA. Global strategy for asthma management and prevention. 2018.
2. Martinez FD, Vercelli D. Asthma. Lancet (London, England). 2013;382(9901):1360-72.
3. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster Analysis and Clinical Asthma Phenotypes. American Journal of Respiratory and Critical Care Medicine. 2008;178(3):218-24.
4. Shaw D, Green R, Berry M, Mellor S, Hargadon B, Shelley M, et al. A cross-sectional study of patterns of airway dysfunction, symptoms and morbidity in primary care asthma. Primary Care Respiratory Journal. 2012;21:283.
5. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet (London, England). 2018;391(10118):350-400.
6. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: A national clinical guideline. 2019.
7. NICE. Asthma: Diagnosis, monitoring and chronic asthma management. National Institute for Health and Care Excellence; 2017. Report No.: NG80.
8. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nature Medicine. 2012;18:716.
9. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Respiratory Medicine. 2017;5(9):691-706.
10. Asthma UK. Asthma facts and statistics [Web page]. England2017 [Facts and statistics about asthma]. Available from: https://www.asthma.org.uk/about/media/facts-and-statistics/.
11. Department of Health. An outcomes strategy for COPD and Asthma: NHS companion document. 2012. Contract No.: 17337.
12. Levy ML, Andrews R, Buckingham R, Evans H, Francis C, Houston R, et al. Why asthma still kills: The National Review of Asthma Deaths (NRAD). Confidential enquiry report. 2014.

13. Walter MJ, Holtzman MJ. A Centennial History of Research on Asthma Pathogenesis. American Journal of Respiratory Cell and Molecular Biology. 2005;32(6):483-9.
14. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Resp J. 2016;47(2):410-9.
15. Heaney LG, Robinson DS. Severe asthma treatment: need for characterising patients. Lancet (London, England). 2005;365(9463):974-6.
16. Frew AJ, Doffman S. Respiratory disease. In: Kumar P, Clark M, editors. Clinical Medicine. 8th ed. Spain: Elsevier; 2012. p. 791-866.
17. Martin E, editor. phenotype. 9th Edition ed: Oxford University Press; 2015.
18. Kuo CS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al. A Transcriptome-driven Analysis of Epithelial Brushings and Bronchial Biopsies to Define Asthma Phenotypes in U-BIOPRED. American Journal of Respiratory and Critical Care Medicine. 2017;195(4):443-55.
19. Loza MJ, Djukanovic R, Chung KF, Horowitz D, Ma K, Branigan P, et al. Validated and longitudinally stable asthma phenotypes based on cluster analysis of the ADEPT study. Respir Res. 2016;17(1):165.
20. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. The European respiratory journal. 2015;46(5):1308-21.
21. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Resp J. 2014;43(2):343-73.
22. Simpson AJ, Hekking P-P, Shaw DE, Fleming LJ, Roberts G, Riley JH, et al. Treatable traits in the European U-BIOPRED adult asthma cohorts. Allergy. 2019;74(2):406-11.
23. Levy ML. The national review of asthma deaths: What did we learn and what needs to change? Breathe. 2015;11(1):15-24.
24. GINA. Global strategy for asthma management and prevention. 2019.
25. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. American Journal of Respiratory and Critical Care Medicine. 2019;201(3):276-93.

26. Peters MC, Wenzel SE. Intersection of biology and therapeutics: type 2 targeted therapeutics for adult asthma. Lancet (London, England). 2020;395(10221):371-83.
27. Nair P, Pizzichini MMM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia. New England Journal of Medicine. 2009;360(10):985-93.
28. Canonica GW. Treating Asthma as an Inflammatory Disease. Chest. 2006;130(1, Supplement):21S-8S.
29. Byrne P, Fabbri LM, Pavord ID, Papi A, Petruzzelli S, Lange P. Asthma progression and mortality: the role of inhaled corticosteroids. Eur Resp J. 2019;54(1):1900491.
30. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-Dose Inhaled Corticosteroids and the Prevention of Death from Asthma. New England Journal of Medicine. 2000;343(5):332-6.
31. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002;57(10):880-4.
32. Williams LK, Peterson EL, Wells K, Ahmedani BK, Kumar R, Burchard EG, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid non-adherence. The Journal of Allergy and Clinical Immunology. 2011;128(6):1185-91.e2.
33. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. Journal of Allergy and Clinical Immunology. 2004;114(6):1288-93.
34. NHS England. Specialised Respiratory Services (adult) – Severe Asthma. 2017.
35. Sabaté E. Adherence to long-term therapies: evidence for action. Switzerland: World Health Organization; 2003.
36. Vrijens B, Dima AL, Van Ganse E, van Boven JFM, Eakin MN, Foster JM, et al. What We Mean When We Talk About Adherence in Respiratory Medicine. The journal of allergy and clinical immunology In practice. 2016;4(5):802-12.
37. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clinic proceedings. 2011;86(4):304-14.
38. Osterberg L, Blaschke T. Adherence to medication. New England Journal of Medicine. 2005;353(5):487-97.

39. Steiner JF, Earnest MA. The Language of Medication-Taking. Annals of internal medicine. 2000;132(11):926-30.
40. Vrijens B, Urquhart J, White D. Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence. Expert Rev Clin Pharmacol. 2014;7(5):633-44.
41. Christensen A, Christrup LL, Fabricius PE, Chrostowska M, Wronka M, Narkiewicz K, et al. The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. J Hypertens. 2010;28(1):194-200.
42. Cos Ho. Decorum. In: Heraclitus oE, editor. Hippocrates [electronic resource]: Prognostic Regimen in Acute Diseases The Sacred Disease The Art Breaths Law Decorum Physician (Ch 1) Dentition II. Cambridge, MA: Harvard University Press; 460-390BC (translated 1923).
43. Horne R. Adherence to treatment. In: Baum A, McManus C, Weinman J, Wallston K, West R, Newman S, et al., editors. Cambridge Handbook of Psychology, Health and Medicine. 2 ed. Cambridge: Cambridge University Press; 2007. p. 415-21.
44. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Archives of internal medicine. 2007;167(6):540-50.
45. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200-9.
46. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. The Cochrane database of systematic reviews. 2017;4:CD012226.
47. O'Byrne PM, Reddel HK, Colice GL. Does the current stepwise approach to asthma pharmacotherapy encourage over-treatment? Respirology (Carlton, Vic). 2010;15(4):596-602.
48. Holt S, Herxheimer A, Suder A, Weatherall M, Cheng S, Shirtcliffe P, et al. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis; Commentary: Dosage needs systematic and critical review. British Medical Journal. 2001;323(7307):253.

49. Masoli M, Weatherall M, Holt S, Beasley R. Clinical dose-response relationship of fluticasone propionate in adults with asthma. Thorax. 2004;59(1):16-20.
50. Barnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. Respiratory care. 2015;60(3):455-68.
51. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. American Journal of Respiratory and Critical Care Medicine. 1994;149(2 Pt 2):S69-76; discussion S7-8.
52. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? Annals of Allergy, Asthma and Immunology. 1997;79(3):177-85; quiz 85-6.
53. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. Chest. 2006;130(1 Suppl):65S-72S.
54. Foster JM, Smith L, Bosnic-Anticevich SZ, Usherwood T, Sawyer SM, Rand CS, et al. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. Internal medicine journal. 2012;42(6):e136-44.
55. Ahmedani B, Peterson E, Wells K, Rand C, Williams L. Asthma medication adherence: the role of God and other health locus of control factors2013; 110(2):[75-9.e2 pp.].
56. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. The Journal of Allergy and Clinical Immunology. 2003;111(6):1219-26.
57. Byer B, Myers LB. Psychological correlates of adherence to medication in asthma. Psychology, Health & Medicine. 2000;5(4):389-93.
58. Clerisme-Beaty EM, Bartlett SJ, Teague WG, Lima J, Irvin CG, Cohen R, et al. The Madison Avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. The Journal of Allergy and Clinical Immunology. 2011;127(2):406-11.
59. Horne R, Weinman J. Self-regulation and Self-management in Asthma: Exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. Psychology & Health. 2002;17(1):17-32.
60. Le TT, Bilderback A, Bender B, Wamboldt FS, Turner CF, Rand CS, et al. Do asthma medication beliefs mediate the relationship between minority status and adherence to therapy? The Journal of asthma :

official journal of the Association for the Care of Asthma. 2008;45(1):33-7.
61. Menckeberg TT, Bouvy ML, Bracke M, Kaptein AA, Leufkens HG, Raaijmakers JA, et al. Beliefs about medicines predict refill adherence to inhaled corticosteroids. Journal of Psychosomatic Research. 2008;64(1):47-54.
62. Wells K, Pladevall M, Peterson EL, Campbell J, Wang M, Lanfear DE, et al. Race-Ethnic Differences in Factors Associated with Inhaled Steroid Adherence among Adults with Asthma. 2008;178(12):1194-201.
63. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. American Journal of Respiratory and Critical Care Medicine. 2009;180(9):817-22.
64. Williams LK, Joseph CL, Peterson EL, Moon C, Xi H, Krajenta R, et al. Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids. Journal of Allergy and Clinical Immunology. 2007;119(1):168-75.
65. Fiese BH, Wamboldt FS, Anbar RD. Family asthma management routines: connections to medical adherence and quality of life. The Journal of pediatrics. 2005;146(2):171-6.
66. Irvine L, Crombie IK, Alder EM, Neville RG, Clark RA. What predicts poor collection of medication among children with asthma? A case-control study. Eur Resp J. 2002;20(6):1464-9.
67. Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. Journal of Allergy and Clinical Immunology. 2007;119(4):811-6.
68. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. Journal of Allergy and Clinical Immunology. 2014;134(6):1260-8.e3.
69. Morton RW, Elphick HE, Rigby AS, Daw WJ, King DA, Smith LJ, et al. STAAR: a randomised controlled trial of electronic adherence monitoring with reminder alarms and feedback to improve clinical outcomes for children with asthma. Thorax. 2017;72(4):347-54.
70. Vasbinder EC, Goossens LM, Rutten-van Molken MP, de Winter BC, van Dijk L, Vulto AG, et al. e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC): a randomised controlled trial. Eur Resp J. 2016;48(3):758-67.

71. Chan AH, Stewart AW, Harrison J, Camargo CA, Jr., Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. The Lancet Respiratory Medicine. 2015;3(3):210-9.
72. Sanchis J, Gich I, Pedersen S. Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? Chest. 2016;150(2):394-406.
73. Price DB, Roman-Rodriguez M, McQueen RB, Bosnic-Anticevich S, Carter V, Gruffydd-Jones K, et al. Inhaler Errors in the CRITIKAL Study: Type, Frequency, and Association with Asthma Outcomes. The journal of allergy and clinical immunology In practice. 2017;5(4):1071-+.
74. 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;4(5):900-9.e2.
75. Bosnic-Anticevich S, Callan C, Chrystyn H, Lavorini F, Nikolaou V, Kritikos V, et al. Inhaler technique mastery and maintenance in healthcare professionals trained on different devices. The Journal of asthma : official journal of the Association for the Care of Asthma. 2018;55(1):79-88.
76. De Tratto K, Gomez C, Ryan CJ, Bracken N, Steffen A, Corbridge SJ. Nurses' knowledge of inhaler technique in the inpatient hospital setting. Clinical nurse specialist CNS. 2014;28(3):156-60.
77. Renwick L. The reality of asthma care in the UK: Annual asthma survey 2018 report. 2018.
78. Dekker FW, Dieleman FE, Kaptein AA, Mulder JD. Compliance with pulmonary medication in general practice. Eur Resp J. 1993;6(6):886.
79. Donnelly JE, Donnelly WJ, Thong YH. Inadequate parental understanding of asthma medications. Annals of allergy. 1989;62(4):337-41.
80. Plaza V, Giner J, Calle M, Rytilä P, Campo C, Ribó P, et al. Impact of patient satisfaction with his or her inhaler on adherence and asthma control. Allergy Asthma Proc. 2018;39(6):437-44.
81. Price D, Harrow B, Small M, Pike J, Higgins V. Establishing the relationship of inhaler satisfaction, treatment adherence, and patient outcomes: a prospective, real-world, cross-sectional survey of US

adult asthma patients and physicians. World Allergy Organ J. 2015;8(1):26-.
82. Small M, Anderson P, Vickers A, Kay S, Fermer S. Importance of inhaler-device satisfaction in asthma treatment: real-world observations of physician-observed compliance and clinical/patient-reported outcomes. Adv Ther. 2011;28(3):202-12.
83. Kripalani S, Henderson LE, Jacobson TA, Vaccarino V. Medication use among inner-city patients after hospital discharge: patient-reported barriers and solutions. Mayo Clinic proceedings. 2008;83(5):529-35.
84. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health. 1999;14(1):1-24.
85. Hahn SR, Park J, Skinner EP, Yu-Isenberg KS, Weaver MB, Crawford B, et al. Development of the ASK-20 Adherence Barrier Survey*. Current Medical Research and Opinion. 2008;24(7):2127-38.
86. Matza LS, Park J, Coyne KS, Skinner EP, Malley KG, Wolever RQ. Derivation and Validation of the ASK-12 Adherence Barrier Survey. Annals of Pharmacotherapy. 2009;43(10):1621-30.
87. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
88. Cluley S, Cochrane GM. Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids. Respiratory medicine. 2001;95(1):37-9.
89. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67-74.
90. Cohen JL, Mann DM, Wisnivesky JP, Home R, Leventhal H, Musumeci-Szabo TJ, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Annals of Allergy Asthma & Immunology. 2009;103(4):325-31.
91. Cole S, Seale C, Griffiths C. 'The blue one takes a battering' why do young adults with asthma overuse bronchodilator inhalers? A qualitative study. BMJ open. 2013;3(2):e002247.
92. Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Resp J. 1994;7(9):1602-9.

93. Crane J, Pearce N, Burgess C, Beasley R. Asthma and the beta agonist debate. Thorax. 1995;50 Suppl 1:S5-10.
94. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. New England Journal of Medicine. 1992;326(8):501-6.
95. Patel M, Pilcher J, Hancox RJ, Sheahan D, Pritchard A, Braithwaite I, et al. The use of beta2-agonist therapy before hospital attendance for severe asthma exacerbations: a post-hoc analysis. NPJ Prim Care Respir Med. 2015;25:14099.
96. Patel M, Pilcher J, Munro C, Hosking A, Pritchard A, Shaw D, et al. Short-acting beta-agonist use as a marker of current asthma control. The journal of allergy and clinical immunology In practice. 2013;1(4):370-7.
97. Martin MJ, Harrison TW. Is it time to move away from short-acting beta-agonists in asthma management? Eur Resp J. 2019;53(4):1802223.
98. Muneswarao J, Hassali MA, Ibrahim B, Saini B, Ali IAH, Verma AK. It is time to change the way we manage mild asthma: an update in GINA 2019. Respir Res. 2019;20(1):183-.
99. Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. Eur Resp J. 2018;51(1).
100. Onyirimba F, Apter A, Reisine S, Litt M, McCusker C, Connors M, et al. Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. Annals of Allergy, Asthma and Immunology. 2003;90(4):411-5.
101. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. The Lancet Respiratory medicine. 2013;1(1):32-42.
102. Ofman JJ, Badamgarav E, Henning JM, Knight K, Gano AD, Jr., Levan RK, et al. Does disease management improve clinical and economic outcomes in patients with chronic diseases? A systematic review. American Journal Medicine. 2004;117(3):182-92.

103. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews. 2008(2).
104. Dean AJ, Walters J, Hall A. A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. Archives of disease in childhood. 2010;95(9):717-23.
105. Lam WY, Fresco P. Medication Adherence Measures: An Overview. BioMed Research International. 2015;2015:217047.
106. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. Primary Care Respiratory Journal. 2009;18:300.
107. Patel M, Perrin K, Pritchard A, Williams M, Wijesinghe M, Weatherall M, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. Respirology (Carlton, Vic). 2013;18(3):546-52.
108. Jentzsch NS, Camargos PA, Colosimo EA, Bousquet J. Monitoring adherence to beclomethasone in asthmatic children and adolescents through four different methods. Allergy. 2009;64(10):1458-62.
109. Gerald JK, Fisher JM, Brown MA, Clemens CJ, Moore MA, Carvajal SC, et al. School-supervised use of a once-daily inhaled corticosteroid regimen: A cluster randomized trial. The Journal of allergy and clinical immunology. 2019;143(2):755-64.
110. Salazar G, Tarwala G, Reznik M. School-based supervised therapy programs to improve asthma outcomes: current perspectives. Journal of asthma and allergy. 2018;11:205-15.
111. Pearce CJ, Fleming L. Adherence to medication in children and adolescents with asthma: methods for monitoring and intervention. Expert Rev Clin Immunol. 2018;14(12):1055-63.
112. Heaney LG, Busby J, Bradding P, Chaudhuri R, Mansur AH, Niven R, et al. Remotely Monitored Therapy and Nitric Oxide Suppression Identifies Nonadherence in Severe Asthma. American Journal of Respiratory and Critical Care Medicine. 2019;199(4):454-64.
113. Howard S, Lang A, Patel M, Sharples S, Shaw D. Electronic monitoring of adherence to inhaled medication in asthma. Current Respiratory Medicine Reviews. 2014;10(1):50-63.
114. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. British Medical Journal. 2011;343:d5928.

115. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. P T. 2008;33(12):700-11.
116. Zlowodzki M, Poolman RW, Kerkhoffs GM, Tornetta P, 3rd, Bhandari M, International Evidence-Based Orthopedic Surgery Working G. How to interpret a meta-analysis and judge its value as a guide for clinical practice. Acta Orthop. 2007;78(5):598-609.
117. PRISMA Statement [Available from: http://www.prisma-statement.org/.
118. Apter A, Wang X, Bogen D, Rand C, McElligott S, Polsky D, et al. Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial2011; 128(3):[516-23.e1 pp.].
119. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. Adherence with twice-daily dosing of inhaled steroids: Socioeconomic and health-belief differences. American Journal of Respiratory and Critical Care Medicine. 1998;157(6 I):1810-7.
120. Bender B, Apter A, Bogen D, Dickinson P, Fisher L, Wamboldt F, et al. Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma2010; 23(2):[159-65 pp.].
121. Berg J, Dunbar-Jacob J, Sereika SM. An evaluation of a self-management program for adults with asthma. Clinical nursing research. 1997;6(3):225-38.
122. Bosley CM, Parry DT, Cochrane GM. PATIENT COMPLIANCE WITH INHALED MEDICATION - DOES COMBINING BETA-AGONISTS WITH CORTICOSTEROIDS IMPROVE COMPLIANCE. Eur Resp J. 1994;7(3):504-9.
123. D'Arcy S, MacHale E, Seheult J, Holmes MS, Hughes C, Sulaiman I, et al. A method to assess adherence in inhaler use through analysis of acoustic recordings of inhaler events. PloS one. 2014;9(6):e98701-e.
124. Goeman D, Jenkins C, Crane M, Paul E, Douglass J. Educational intervention for older people with asthma: a randomised controlled trial2013; 93(3):[586-95 pp.].
125. Janson S, McGrath K, Covington J, Baron R, Lazarus S. Objective airway monitoring improves asthma control in the cold and flu season: a cluster randomized trial2010; 138(5):[1148-55 pp.].
126. Janson SL, McGrath KW, Covington JK, Cheng SC, Boushey HA. Individualized asthma self-management improves medication

adherence and markers of asthma control. Journal of Allergy and Clinical Immunology. 2009;123(4):840-6.
127. Krishnan JA, Riekert KA, McCoy JV, Stewart DY, Schmidt S, Chanmugam A, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. American Journal of Respiratory and Critical Care Medicine. 2004;170(12):1281-5.
128. Lacasse Y, Archibald H, Ernst P, Boulet LP. Patterns and determinants of compliance with inhaled steroids in adults with asthma. Canadian respiratory journal. 2005;12(4):211-7.
129. Mann M, Eliasson O, Patel K, ZuWallack RL. A comparison of the effects of bid and qid dosing on compliance with inhaled flunisolide. Chest. 1992;101(2):496-9.
130. Mann MC, Eliasson O, Patel K, ZuWallack RL. An evaluation of severity-modulated compliance with q.i.d. dosing of inhaled beclomethasone. Chest. 1992;102(5):1342-6.
131. Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, et al. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. Annals of allergy. 1991;66(4):294-9.
132. McGann EF, Sexton D, Chyun DA. Denial and compliance in adults with asthma. Clinical nursing research. 2008;17(3):151-70.
133. Perrin KWMWMJKWMBR. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting ?-agonist inhaler therapy in asthma. Journal of Allergy and Clinical Immunology. 2010;126(3):505.
134. Plaza V, Fernandez-Rodriguez C, Cosio BG, Entrenas LM, De Llano LP, Gutierrez-Pereyra F, et al. Validation of the 'Test of the Adherence to Inhalers' (TAI) for Asthma and COPD Patients. Journal of aerosol medicine and pulmonary drug delivery. 2016;29(2):142-52.
135. Rand C, Bilderback A, Schiller K, Edelman J, Hustad C, Zeiger R. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial2007; 119(4):[916-23 pp.].
136. Van Der Palen J, Klein JJ, Rovers MM. Compliance with inhaled medication and self-treatment guidelines following a self-management programme in adult asthmatics. Eur Resp J. 1997;10(3):652-7.
137. Wells KE, Cajigal S, Peterson EL, Ahmedani BK, Kumar R, Lanfear DE, et al. Assessing differences in inhaled corticosteroid response by self-reported race-ethnicity and genetic ancestry among asthmatic

subjects. Journal of Allergy and Clinical Immunology. 2016;137(5):1364.
138. Yeung M, O'Connor SA, Parry DT, Cochrane GM. Compliance with prescribed drug therapy in asthma. Respiratory medicine. 1994;88(1):31-5.
139. Chmelik F, Doughty A. Objective measurements of compliance in asthma treatment. Annals of allergy. 1994;73(6):527-32.
140. Weinstein AG, Singh A, Laurenceau JP, Skoner DP, Maiolo J, Sharara R, et al. A Pilot Study of the Effect of an Educational Web Application on Asthma Control and Medication Adherence. The journal of allergy and clinical immunology In practice. 2019.
141. Weinstein AG, Singh A, Laurenceau J-P, Skoner DP, Maiolo J, Sharara R, et al. A Pilot Study of the Effect of an Educational Web Application on Asthma Control and Medication Adherence. The journal of allergy and clinical immunology In practice. 2019;7(5):1497-506.
142. 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 of the American Thoracic Society. 2016;13(11):1894-903.
143. Porta M, Last JM. Hawthorne effect. A Dictionary of Public Health. 2nd edition ed: Oxford University Press; 2018.
144. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836-44.
145. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A Long-term Study of the Antiinflammatory Effect of Low-dose Budesonide Plus Formoterol versus High-dose Budesonide in Asthma. American Journal of Respiratory and Critical Care Medicine. 2000;161(3):996-1001.
146. Ställberg B, Nyström Kronander U, Olsson P, Gottberg L, Rönmark E, Lundbäck B. Living with asthma in Sweden—the ALMA study. Respiratory medicine. 2003;97(7):835-43.
147. de Marco R, Cazzoletti L, Cerveri I, Corsico A, Bugiani M, Accordini S, et al. Are the asthma guideline goals achieved in daily practice? A population-based study on treatment adequacy and the control of asthma. Int Arch Allergy Immunol. 2005;138(3):225-34.

148. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC pulmonary medicine. 2006;6:13.
149. Breekveldt-Postma NS, Koerselman J, Erkens JA, van der Molen T, Lammers JW, Herings RM, et al. Treatment with inhaled corticosteroids in asthma is too often discontinued. Pharmacoepidemiol Drug Saf. 2008;17(4):411-22.
150. Boushey HA. Effects of inhaled corticosteroids on the consequences of asthma. Journal of Allergy and Clinical Immunology. 1998;102(4, Supplement):S5-S16.
151. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. The Journal of allergy and clinical immunology. 2001;107(6):937-44.
152. Blakey JD, Clift J. Smart Asthma. Asthma UK; 2017.
153. Clift J. Connected asthma: how technology will transform care. Asthma UK; 2016.
154. NICE. Smartinhaler for asthma. 2017.
155. Price D, Brusselle G, Roche N, Freeman D, Chisholm A. Real-world research and its importance in respiratory medicine. Breathe. 2015;11(1):26-38.
156. Burgess SW, Sly PD, Devadason SG. Providing feedback on adherence increases use of preventive medication by asthmatic children. The Journal of asthma : official journal of the Association for the Care of Asthma. 2010;47(2):198-201.
157. Kuipers E, Wensing M, de Smet P, Teichert M. Self-management research of asthma and good drug use (SMARAGD study): a pilot trial. International journal of clinical pharmacy. 2017:1-9.
158. Kenyon CC, Gruschow SM, Quarshie WO, Griffis H, Leach MC, Zorc JJ, et al. Controller adherence following hospital discharge in high risk children: A pilot randomized trial of text message reminders. The Journal of asthma : official journal of the Association for the Care of Asthma. 2018:1-9.
159. Sulaiman I, Mac Hale E, Holmes M, Hughes C, D'Arcy S, Taylor T, et al. 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. BMJ open. 2016;6(1):e009350.

160. Adams SA, Leach MC, Feudtner C, Miller VA, Kenyon CC. Automated Adherence Reminders for High Risk Children With Asthma: A Research Protocol. JMIR Res Protoc. 2017;6(3):e48.
161. McCullough AR, Ryan C, Macindoe C, Yii N, Bradley JM, O'Neill B, et al. Behavior change theory, content and delivery of interventions to enhance adherence in chronic respiratory disease: A systematic review. Respiratory medicine. 2016;116:78-84.
162. Bender B, Milgrom H, Apter A. Adherence intervention research: what have we learned and what do we do next? Journal of Allergy and Clinical Immunology. 2003;112(3):489-94.
163. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. The journal of allergy and clinical immunology In practice. 2013;1(1):83-91.
164. Patel MPJPAPKTJSDHSHMBPWMBR. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: A randomised controlled trial. The Lancet Respiratory Medicine. 2013;1(1):32.
165. Pilcher J, Holliday M, Ebmeier S, McKinstry S, Messaoudi F, Weatherall M, et al. Validation of a metered dose inhaler electronic monitoring device: implications for asthma clinical trial use. BMJ Open Respiratory Research. 2016;3(1):e000128.
166. Pilcher J, Shirtcliffe P, Patel M, McKinstry S, Cripps T, Weatherall M, et al. Three-month validation of a turbuhaler electronic monitoring device: implications for asthma clinical trial use. BMJ Open Respiratory Research. 2015;2(1):e000097.
167. Burgess SW, Wilson SS, Cooper DM, Sly PD, Devadason SG. In vitro evaluation of an asthma dosing device: the smart-inhaler. Respiratory medicine. 2006;100(5):841-5.
168. Foster JM, Smith L, Usherwood T, Sawyer SM, Rand CS, Reddel HK. The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers. The Journal of asthma : official journal of the Association for the Care of Asthma. 2012;49(6):657-62.
169. Patel M, Pilcher J, Chan A, Perrin K, Black P, Beasley R. Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: implications for asthma clinical trial use. Journal of Allergy and Clinical Immunology. 2012;130(6):1420-2.

170. Adejumo I, Shaw DE. Electronic Monitoring Devices as an Intervention in Asthma: The Story So Far. Current Respiratory Medicine Reviews. 2018;14(1):5-22.
171. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. Journal of Allergy and Clinical Immunology. 2006;117(3):549-56.
172. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. Journal of Allergy and Clinical Immunology. 2009;124(4):719-23.e1.
173. Wilson SR, Rand CS, Cabana MD, Foggs MB, Halterman JS, Olson L, et al. Asthma outcomes: quality of life. Journal of Allergy and Clinical Immunology. 2012;129(3 Suppl):S88-123.
174. British National Formulary. British National Formulary: Salbutamol London, UK: BMJ Group; Pharmaceutical Press; 2019 [
175. British National Formulary. British National Formulary: Terbutaline London, UK: BMJ Group; Pharmaceutical Press; 2019 [
176. Al Sallakh MA, Vasileiou E, Rodgers SE, Lyons RA, Sheikh A, Davies GA. Defining asthma and assessing asthma outcomes using electronic health record data: a systematic scoping review. Eur Resp J. 2017;49(6).
177. Gliklich RE, Leavy MB, Li F. AHRQ Methods for Effective Health Care. Standardized Library of Asthma Outcome Measures. Rockville (MD): Agency for Healthcare Research and Quality (US); 2019.
178. Chan AH, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. The journal of allergy and clinical immunology In practice. 2013;1(5):446-54.
179. van Boven JFM, Trappenburg JCA, van der Molen T, Chavannes NH. Towards tailored and targeted adherence assessment to optimise asthma management. NPJ Prim Care Respir Med. 2015;25:15046-.
180. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Resp J. 2015;45(2):396.
181. Burgess SW, Sly PD, Morawska A, Devadason SG. Assessing adherence and factors associated with adherence in young children with asthma. Respirology (Carlton, Vic). 2008;13(4):559-63.

182. Lycett H, Wildman E, Raebel EM, Sherlock JP, Kenny T, Chan AHY. Treatment perceptions in patients with asthma: Synthesis of factors influencing adherence. Respiratory medicine. 2018;141:180-9.
183. Miles C, Arden-Close E, Thomas M, Bruton A, Yardley L, Hankins M, et al. Barriers and facilitators of effective self-management in asthma: systematic review and thematic synthesis of patient and healthcare professional views. NPJ Prim Care Respir Med. 2017;27(1):57.
184. Foster JM, Reddel HK, Usherwood T, Sawyer SM, Smith L. Patient-perceived acceptability and behaviour change benefits of inhaler reminders and adherence feedback: A qualitative study. Respiratory medicine. 2017;129:39-45.
185. Howard S, Lang A, Sharples S, Shaw D. See I told you I was taking it! – Attitudes of adolescents with asthma towards a device monitoring their inhaler use: Implications for future design. Applied Ergonomics. 2017;58:224-37.
186. Stewart AC, Gannon KN, Beresford F, Fleming L. Adolescent and caregivers' experiences of electronic adherence assessment in paediatric problematic severe asthma. Journal of child health care : for professionals working with children in the hospital and community. 2018;22(2):238-50.
187. Amico KR, Mugavero M, Krousel-Wood MA, Bosworth HB, Merlin JS. Advantages to Using Social-Behavioral Models of Medication Adherence in Research and Practice. Journal of General Internal Medicine. 2018;33(2):207-15.
188. Munro S, Lewin S, Swart T, Volmink J. A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? BMC public health. 2007;7:104.
189. Holmes EAF, Hughes DA, Morrison VL. Predicting Adherence to Medications Using Health Psychology Theories: A Systematic Review of 20 Years of Empirical Research. Value in Health. 2014;17(8):863-76.
190. Leventhal H, Cameron L. Behavioral theories and the problem of compliance. Patient education and counseling. 1987;10(2):117-38.
191. Lincoln Y, Lynham S, Guba E. Paradigmatic controversies, contradictions, and emerging confluences, revisited. In: Denzin N, Lincoln Y, editors. The SAGE Handbook of Qualitative Research. USA: SAGE Publications; 2018. p. p. 108.

192. Denzin N, Lincoln Y. Introduction. In: Denzin N, Lincoln Y, editors. The SAGE Handbook of Qualitative Research. USA: SAGE Publications, Inc; 2018. p. 1.
193. Spradley J. The ethnographic interview. Long Grove, Illinois: Waveland Press, Inc; 1979.
194. Jones R. Why do qualitative research? British Medical Journal. 1995;311(6996):2.
195. Loder E, Groves T, Schroter S, Merino JG, Weber W. Qualitative research and The BMJ. British Medical Journal. 2016;352:i641.
196. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. British Medical Journal. 2015;350:h1258.
197. Oxford R. Constructivism: Shape-shifting, substance, and teacher education applications. Peabody Journal of Education. 1997;72(1):35-66.
198. Peck B, Mummery J. Hermeneutic Constructivism: An Ontology for Qualitative Research. Qualitative health research. 2018;28(3):389-407.
199. Brinkmann S. The interview. In: Denzin N, Lincoln Y, editors. The SAGE Handbook of Qualitative Research. Fifth edition ed. USA: SAGE Publications, Inc; 2018. p. p. 576.
200. Yeo A, Legard R, Keegan J, Ward K, McNaughton Nicholls C, Lewis J. In-depth interviews. In: Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R, editors. Qualitative Research Practice. London, UK: SAGE Publications Ltd; 2014. p. 178.
201. King N, Horrocks C. Carrying out qualitative interviews. Interviews in Qualitative Research. First ed. London, UK: SAGE Publications Ltd.; 2010. p. 44-7.
202. Spencer L, Ritchie J, Ormston R, O'Connor W, Barnard M. Analysis: Principles and Processes. In: Ritchie J, Lewis J, McNaughton Nicholls C, Ormston R, editors. Qualitative Research Practice: A Guide for Social Science Students and Researchers. Second Edition ed: SAGE Publications, Inc; 2014.
203. Koro-Ljunberg M, MacLure M, Ulmer J. D...a...t...a..., Data++, Data, and Some Problematics. In: Denzin N, Lincoln Y, editors. The SAGE Handbook of Qualitative Research. Fifth Edition ed. USA: SAGE Publications, Inc; 2018.

204. Rae J, Green B. Portraying Reflexivity in Health Services Research. Qualitative health research. 2016;26(11):1543-9.
205. Mitchell J, Boettcher-Sheard N, Duque C, Lashewicz B. Who Do We Think We Are? Disrupting Notions of Quality in Qualitative Research. Qualitative health research. 2018;28(4):673-80.
206. Mauthner NS, Doucet A. Reflexive Accounts and Accounts of Reflexivity in Qualitative Data Analysis. Sociology. 2003;37(3):413-31.
207. Farnesi BC, Ducharme FM, Blais L, Collin J, Lavoie KL, Bacon SL, et al. Guided asthma self-management or patient self-adjustment? Using patients' narratives to better understand adherence to asthma treatment. Patient Preference and Adherence. 2019;13:587-97.
208. Simpson AJ, Honkoop PJ, Kennington E, Snoeck-Stroband Jiska B, Smith I, East J, et al. Perspectives of patients and healthcare professionals on mHealth for asthma self-management. Eur Resp J. 2017;49(5):1601966.
209. Venkataramanan R, Thirunarayan K, Jaimini U, Kadariya D, Yip HY, Kalra M, et al. Determination of Personalized Asthma Triggers From Multimodal Sensing and a Mobile App: Observational Study. JMIR pediatrics and parenting. 2019;2(1):e14300.
210. Honkoop PJ, Simpson A, Bonini M, Snoeck-Stroband JB, Meah S, Fan Chung K, et al. MyAirCoach: the use of home-monitoring and mHealth systems to predict deterioration in asthma control and the occurrence of asthma exacerbations; study protocol of an observational study. BMJ open. 2017;7(1):e013935-e.
211. Hodson H. Revealed: Google AI has access to huge haul of NHS patient data. New Scientist. 2016 29/04/2016.
212. Huckvale K, Morrison C, Ouyang J, Ghaghda A, Car J. The evolution of mobile apps for asthma: an updated systematic assessment of content and tools. BMC medicine. 2015;13:58.
213. Huckvale K. Apps for asthma self-management: a systematic assessment of content and tools. BioMed Central Medicine. 2012;10(144).
214. Huckvale K, Wang CJ, Majeed A, Car J. Digital health at fifteen: more human (more needed). BMC medicine. 2019;17(1):62-.
215. Cvrkel T. The ethics of mHealth: Moving forward. Journal of dentistry. 2018;74 Suppl 1:S15-s20.

216. Hansson Scherman M, Lowhagen O. Drug compliance and identity: reasons for non-compliance. Experiences of medication from persons with asthma/allergy. Patient education and counseling. 2004;54(1):3-9.
217. Gamble J, Fitzsimons D, Lynes D, Heaney LG. Difficult asthma: people's perspectives on taking corticosteroid therapy. Journal of clinical nursing. 2007;16(3a):59-67.
218. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. Lancet (London, England). 2014;383(9928):1581-92.
219. Li N, Georas S, Alexis N, Fritz P, Xia T, Williams MA, et al. A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): Why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects. Journal of Allergy and Clinical Immunology. 2016;138(2):386-96.
220. Laville S. Ella Kissi-Debrah: new inquest granted into 'air pollution' death. The Guardian. 2019 02/05/2019.
221. Gupta RP, Mukherjee M, Sheikh A, Strachan DP. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. Thorax. 2018;73(8):706.
222. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. Current opinion in allergy and clinical immunology. 2009;9(2):154-60.
223. Forno E, Celedón JC. Health Disparities in Asthma. American Journal of Respiratory and Critical Care Medicine. 2012;185(10):1033-5.
224. Hull SA, McKibben S, Homer K, Taylor SJ, Pike K, Griffiths C. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. NPJ Prim Care Respir Med. 2016;26:16049-.
225. Netuveli G, Hurwitz B, Levy M, Fletcher M, Barnes G, Durham SR, et al. Ethnic variations in UK asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis. Lancet (London, England). 2005;365(9456):312-7.
226. Sheikh A, Steiner MFC, Cezard G, Bansal N, Fischbacher C, Simpson CR, et al. Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. BMC medicine. 2016;14(1):3.

227. Gorman BK, Chu M. Racial and ethnic differences in adult asthma prevalence, problems, and medical care. Ethnicity & Health. 2009;14(5):527-52.
228. Goldman DP, Joyce GF, Escarce JJ, Pace JE, Solomon MD, Laouri M, et al. Pharmacy Benefits and the Use of Drugs by the Chronically Ill. Journal of the American Medical Association. 2004;291(19):2344-50.
229. Berkowitz SA, Seligman HK, Choudhry NK. Treat or eat: food insecurity, cost-related medication underuse, and unmet needs. The American journal of medicine. 2014;127(4):303-10.e3.
230. Apter AJ, Wan F, Reisine S, Bender B, Rand C, Bogen DK, et al. The association of health literacy with adherence and outcomes in moderate-severe asthma. Journal of Allergy and Clinical Immunology. 2013;132(2):321-7.
231. Christensen A, Osterberg LG, Hansen EH. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: a systematic review. J Hypertens. 2009;27(8):1540-51.
232. Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Drug adherence in hypertension: from methodological issues to cardiovascular outcomes. Journal of Hypertension. 2017;35(6):1133-44.
233. Marquez E, Claros N, Gil-Guillén V, Wichmann M, Casado-Martínez J, Pablos J, et al. Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: The EAPACUM-HTA study. Journal of Hypertension. 2006;24:169-75.
234. Rudd P, Miller NH, Kaufman J, Kraemer HC, Bandura A, Greenwald G, et al. Nurse management for hypertension. A systems approach. American journal of hypertension. 2004;17(10):921-7.
235. Knafl GJ, Schoenthaler A, Ogedegbe G. Secondary analysis of electronically monitored medication adherence data for a cohort of hypertensive African-Americans. Patient Preference and Adherence. 2012;6:207-19.
236. van Onzenoort HA, Verberk WJ, Kessels AG, Kroon AA, Neef C, van der Kuy PH, et al. Assessing medication adherence simultaneously by electronic monitoring and pill count in patients with mild-to-moderate hypertension. American journal of hypertension. 2010;23(2):149-54.
237. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1

diabetes: a multicentre, non-masked, randomised controlled trial. Lancet (London, England). 2016;388(10057):2254-63.
238. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2017;8(1):55-73.
239. Leelarathna L, Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabetic medicine : a journal of the British Diabetic Association. 2018;35(4):472-82.
240. Hellmund R, Weitgasser R, Blissett D. Cost Calculation for a Flash Glucose Monitoring System for Adults with Type 2 Diabetes Mellitus Using Intensive Insulin - a UK Perspective. Eur Endocrinol. 2018;14(2):86-92.
241. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes care. 2020;43(9):2153-60.
242. England N. The NHS Long Term Plan. NHS England; 2019.
243. UK; D. Diabetes UK Consensus Guideline for Flash Glucose Monitoring. 2017.
244. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. New England Journal of Medicine. 2018;378(20):1877-87.
245. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. New England Journal of Medicine. 2018;378(10):902-10.
246. Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D, et al. Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. BMJ. 2012;344:e1756.

Appendix A: List of abbreviations

ACQ	Asthma Control Questionnaire
ACT™	Asthma Control Test™
AE	Asthma education
app	Application
AQLQ	Asthma quality of life questionnaire
ASK	Adherence Starts with Knowledge questionnaire
ATS	American Thoracic Society
AVR	Audio-visual reminder
BDP	Beclometasone diproprionate
BMQ	Beliefs About Medication Questionnaire
BTS	British Thoracic Society
C-ACT	Children's Asthma Control Test
CARAT	Control of allergic rhinitis and asthma test
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Centre for Epidemiological Studies Depression Scale
CG	Control group
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
COPD	Chronic obstructive pulmonary disease
DAL	Diskus Adherence Logger
Doser CT	Doser Clinical Trials Version
ED	Emergency department
EMD	Electronic monitoring device
EMI	Electronic monitoring of the intake of inhalation medication
ERS	European Respiratory Society
F_ENO	Fractional exhaled nitric oxide

FEV_1	Forced expiratory volume in one second
GINA	Global initiative for asthma
GP	General practitioner
GPS	Global positioning system
HADS	Hospital anxiety and depression score
HIV	Human immunodeficiency virus
ICS	Inhaler corticosteroid
ID	Identity
IEEE	Institute of Electrical and Electronics Engineers
IG	Intervention group
IgE	Immunoglobulin E
INCA	Inhaler Compliance Assessment
IPQ	Illness Perception Questionnaire
IQR	Interquartile range
IRF	Inhaler reminders and feedback
isCGM	Intermittently scanned continuous glucose monitoring
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
LABA	Long-acting beta agonist
LED	Light-emitting diode
MARS	Medication Adherence Report Scale
MARS-A	Medication Adherence Report Scale for Asthma
MART	Maintenance and reliever therapy
MDI	Metered dose inhaler
MEDLINE	Medical Literature Analysis and Retrieval System Online
mHealth	Mobile health
MID	Minimally important difference
MMAS	Morisky Medication Adherence Scale

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRAD	National Review of Asthma Deaths
NRRD	Nottingham Respiratory Research Database
NRRU	Nottingham Respiratory Research Unit
OCS	Oral corticosteroids
PAD	Personalised adherence discussion
PAQLQ	Paediatric asthma quality of life questionnaire
PDC	Proportion of days covered
PEF	Peak expiratory flow rate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Problem solving approach
RCT	Randomised controlled trial
ROI	Republic of Ireland
rtCGM	Real-time continuous glucose monitoring
SABA	Short-acting beta agonist
SD	Standard deviation
SES	Socioeconomic status
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardised mean difference
SMS	Short message service
TIC	Turbuhaler Inhalation Computer
TX	Texas
U-BIOPRED	Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes
UC	Usual care
USA	United States of America
USB	Universal Serial Bus
WHO	World Health Organisation
WMD	Weighted mean difference

Appendix B: Systematic review protocol

Review Title

Effectiveness of Current Methods of Objectively Assessing Inhaler Adherence in Adults with Asthma: A Systematic Review

Authors

Ireti Adejumo, Tricia M. McKeever, Dominick Shaw

Contacts
Corresponding Author: Ireti Adejumo
Clinical Research Fellow
Department of Respiratory Medicine
University of Nottingham
B35, Clinical Sciences Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 1PB
0115 8231935
msxia6@nottingham.ac.uk
Tricia McKeever
Associate Professor of Statistics
University of Nottingham
Clinical Sciences Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 1PB
Dominick Shaw
Associate Professor of Respiratory Medicine and Honorary Consultant
Department of Respiratory Medicine
University of Nottingham
Clinical Sciences Building
Nottingham City Hospital
Nottingham
NG51PB

General Information

PROSPERO Registration No:	CRD42017057708
Anticipated start date:	03/04/2017
Anticipated completion date:	01/12/2018
Review team contributions:	The review will be carried out by Ireti Adejumo. Tricia McKeever will contribute to the searches, Dominick Shaw will review conflicts. Christos Chalitsios will contribute to data extraction. Both Tricia McKeever and Dominick Shaw will contribute to and review the final document.
Amendments:	Amendments to this protocol will be approved by the whole review team and submitted as an update to the PROSPERO database.
Support and Conflicts of Interest:	The authors have not received specific funding to carry out this review. Ireti Adejumo is a PhD student with the University of Nottingham funded by GSK. Christos Chalitsios is a PhD student with the University of Nottingham. Tricia McKeever is an Associate Professor of Statistics at the University of Nottingham. Dominick Shaw is an Associate Professor of Respiratory Medicine and Honorary Consultant at the University if Nottingham.

Introduction

Background

Non-adherence with inhaled pharmacotherapy, generally manifesting as inhaled corticosteroid (ICS) underuse or short-acting beta agonist (SABA) overuse1, is a well-recognised barrier to adequate control of asthma. As such, it has been linked with increased exacerbation rates2, hospitalisations3 and deaths4. Guidelines advise the assessment of adherence as part of routine asthma care, particularly when considering an escalation of therapy5, 6.

Different modes of assessing adherence include prescription refill counting, canister weighing, dose meter counting and, more recently, the introduction of electronic monitoring with remote feedback. To our knowledge, there has not yet been a systematic review examining the current evidence base for these different modes of assessing adherence.

Treatment modalities are advancing to increase the availability of niche, expensive therapies such as monoclonal antibodies and bronchial thermoplasty, with the potential for a greater side effect profile. This is occurring as the plateau in asthma death rates point to continuing concerns with the standards of basic care provided7. Consequently, it is more essential than ever to

ensure that patients with asthma obtain the maximum possible benefit from the evidence-based care they already receive. It is also important that healthcare professionals involved in asthma care are able to assess adherence effectively, both to avert adverse outcomes for their patients and to inform safe, effective management for ongoing care.

Rationale

This systematic review examines the evidence base for current modes of assessing adherence to inhaled corticosteroids, including novel electronic means. Although other reviews8 have assessed different methods individually, none has sought to systematically review all known objective methods as we are attempting to. It is therefore hoped that this will inform ongoing conversations around what constitutes accurate, effective, and good quality assessment which is feasible in the day-to-day clinical environment, so proving a useful tool for the healthcare providers in asthma.

Objectives

<u>Study 1: A systematic review of electronically monitored adherence in clinical trials</u>

1. To determine electronic monitoring methods for assessing adherence to inhaled corticosteroid therapy in adult asthma used in the literature.

2. To determine the rate of ICS adherence found in the literature using electronically monitored adherence.

3. To describe criteria used to analyse and report the effectiveness of these methods where effectiveness includes accuracy, reliability, change in self-management behaviours or change in clinical outcomes.

4. To attempt to describe some universal criteria for analysing and reporting effectiveness of electronic monitoring methods of assessing adherence to inhaled corticosteroid therapy in asthma.

<u>Study 2: A systematic review of current methods of objectively assessing inhaler adherence in adults with asthma</u>

1. To determine objective methods of assessing adherence to inhaled corticosteroid therapy in adult asthma used in the literature.

2. To determine the effectiveness of these methods when compared with the standard method at the time.

3. To describe criteria used to analyse and report the effectiveness of these methods where effectiveness includes accuracy, reliability, change in self-management behaviours or change in clinical outcomes.

4. To attempt to describe some universal criteria for analysing and reporting effectiveness of methods of assessing adherence to inhaled corticosteroid therapy in asthma.

Methods

Eligibility criteria

Study type

Randomised controlled trials, quasi-experimental studies and cohort studies will be included.

Adherence may be studied as part of a broader intervention. Consequently, any study where the effectiveness of a method of assessing adherence has been considered will be included.

Studies will be limited to those with human participants.

Participants

Studies will be included where the study population have been pre-defined as adults having asthma of any severity. This

review will be limited to adults as management will differ significantly when clinicians deal with adults as opposed to dealing with the child/parent and adolescent dynamics.

Interventions

Any objective (i.e. not self-reported or physician-reported) method of assessing adherence to inhaled therapy including (but not limited to) integrated inhaler device dose counters, prescription assessment, canister weighing and electronic monitoring.

Comparators

Comparators may include other objective methods of assessing adherence or subjective methods of assessing adherence or no assessment of adherence.

Outcomes

Outcomes of accuracy of methods of assessing adherence, change in self-management behaviours or change in clinical outcomes may be reported.

Identification of studies

Electronic searches

Studies will be identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE group of databases, EMBASE, Web of Science, SCOPUS, CINAHL, PsychINFO and IEEE Xplore.

Any unpublished studies where data collection and analysis is complete will be searched for using clinicaltrials.gov, BioMedCentral ISRCTN Registry and OpenGrey.

Literature from 1950 onwards will be searched.

The following search terms will be used:

1. exp Asthma/ OR Asthma*.mp.

2. (exp Nebulizers and Vaporizers/) OR (exp Asthma/dt) OR Inhal* OR Aerosol* OR Nebuli*

AND

(exp Patient Compliance/) OR Adher* OR Complian* OR Co?operat* OR Concord* OR Non?adher* OR Non?complian* OR Non?concord* OR Under?complian* OR Over?complian* OR Monitor*

OR

3. EMD OR Smartinhaler OR SmartTrack OR SmartTouch OR Nebulizer Chrono* OR Doser* OR Propeller OR MDILog OR Canister weigh* OR Prescription count* OR Refill count* OR Dose count*

Data Collection and Analysis

Study Selection

Search Results

Two independent reviewers (IA and TM) will inspect citations retrieved from the searches and identify relevant abstracts for further screening as denoted by the eligibility criteria detailed above. Discrepancies will be discussed with the third reviewer (DS) who will make the final decision on inclusion/exclusion.

Further Screening

Two independent reviewers (IA and TM) will examine identified abstracts to assess further for fulfilment of the eligibility criteria and relevance to the study question. Where abstracts are not obtainable, the full article will be obtained instead. Disagreements will be discussed with the third reviewer (DS) who will make the final decision on inclusion/exclusion.

Full Text

Full texts will be obtained by the investigation team. IA will examine identified full texts for eligibility. TM will examine a 10% sample to check that there is agreement. Disagreements will be discussed with the third reviewer (DS) who will make the final decision on inclusion/exclusion. Where full texts are unavailable, it will be demonstrated that investigators made

every reasonable effort to obtain them and reasons for the unavailability will be documented.

Data Extraction and Management

Data Management

Data will be managed using the Covidence online system (www.covidence.org, © 2017 Covidence, Melbourne).

Data Collection

Data will be extracted onto pre-designed forms which will be tested with a sample of papers for usability.

Extraction will be performed by two reviewers. A third reviewer will also data extract 10% of included studies for validation purposes.

Outcome measures

Primary outcome

Objectively monitored adherence rates in available data.

Suggested gold standard method of assessing inhaler adherence in adults with asthma.

Secondary outcomes

1. Comparative effectiveness of different methods of assessing adherence compared to standard at the time or drawn from this study.
    a. Mean or median difference between assessed method of adherence and gold standard method at the time (if applicable, gold standard previously reported or reported from the study results).
    b. Sensitivity and/or specificity reported for detection of (lack of) adherence.
    c. Positive and/or negative predictive values reported for detection of (lack of) adherence.
    d. Any other measure of accuracy.
    e. Study commentary on evaluation of methods investigated.
        i. Accuracy
        ii. Usefulness
        iii. Accessibility
2. Any reported change in self-management behaviour (including adherence).
3. Any reported change in clinical outcomes.
4. Suggested characteristics of a gold standard method of assessing adherence.

Quality Assessment

Risk of Bias

Risk of bias will be assessed and reported descriptively using the Cochrane Collaboration's tool for assessing risk of bias. The tool has been adapted by the study team to account for risk of bias in observational studies.

Assessment of Heterogeneity

Heterogeneity will be described at the following levels:

1. The method used to assess adherence.
2. The method used to analyse effectiveness.
3. The standard against which effectiveness was assessed.
4. How effectiveness was reported.
5. The context of the study.

Data Synthesis and Statistical Analysis

It is not anticipated that it will be possible to perform a meta-analysis of methods of assessing adherence in this review due to the anticipated small number of studies in this field and the multiple methods of assessment which are heterogeneous in their nature as well as their modes of measurement and

reporting. Instead, a narrative synthesis will be provided based on the context of assessment of adherence, the mode of assessment of adherence, the suitability of that mode for the context in which it was provided, the effectiveness of that mode (whether as denoted by studies using it or by a means of assessing effectiveness derived from this review) and whether there is enough evidence to recommend its use in routine clinical practice.

Potential outcomes for a future meta-analysis may be suggested should common themes occur.

Subgroup Analysis

This review will also separately analyse the primary outcome in the following groups known to be poorly adherent:

- Ethnic minorities
- Low socioeconomic status
- "Difficult" asthma (poorly controlled, severe or resistant)

Any randomised trials directly comparing two or more methods of assessing adherence and any trials directly comparing two or more methods of assessing adherence will also be analysed separately.

Any studies judged as “high quality” will be analysed separately.

Appendix C: Pilot study protocol

Clinical Investigation Title:
IMPROVING ASTHMA TREATMENT USING INHALER TECHNOLOGY

Short Study Title:
INHALER TECHNOLOGY STUDY

A 2-arm feasibility study to assess whether inhaler electronic monitoring and feedback technology is patient-friendly and cost effective in three main areas of asthma care: inhaler adherence, treatment decisions, and the prediction and prevention of asthma exacerbations.

- **This protocol has regard for the HRA guidance**

Sponsor	Nottingham University Hospitals NHS Trust
Funder	GlaxoSmithKline (GSK)
Funding Reference Number	201165
Chief Investigator	Dr Dominick Shaw Respiratory Research Unit University of Nottingham
ISRCTN Number	ISRCTN90986892
REC Reference Number	16/LO/1693
IRAS Reference Number	193750
Sponsor Reference Number	14RM008
Version Number and Date	Version 1.5 date 09 Nov 18

Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust (s), regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Study Statistician:

Signature: Date:

..... …../…./……

Name: (please print)

.....

TABLE OF CONTENTS

24.References

25.Appendices

CLINICAL INVESTIGATION MANAGEMENT GROUP

Chief Investigator	**Co Investigators**
Name: Dr Dominick Shaw Address: Respiratory Research Unit Clinical Sciences Building University of Nottingham Nottingham City Hospital Campus Nottingham NG5 1PB Phone: 0115 8231709 Email: Dominic.shaw@nottingham.ac.uk	Name: Dr Mitesh Patel Address: Chest Clinic, Level 6, Derriford Hospital, Plymouth. PL6 8DH Phone: Email: mitesh.patel@nottingham.ac.uk / mitesh.patel6@nhs.net
Co Investigators	**Clinical Investigation Management**
Name: Dr Tim Harrison Address: Respiratory Research Unit Clinical Sciences Building University of Nottingham Nottingham City Hospital Campus Nottingham NG5 1PB Phone: 0115 8231714 Email: tim.harrison@nottingham.ac.uk	Name: Dr Ireti Adejumo Address: B35 Clinical Sciences Building Nottingham City Hospital Hucknall Road Nottingham NG5 1PB Phone: 0115 82 31935 Email: msxia6@nottingham.ac.uk
Statistician	**Qualitative Data Support**
Name: Dr Tricia McKeever Address: C115 Clinical Sciences Building Nottingham City Hospital Hucknall Road Nottingham NG5 1PB Telephone: 0115 823 1721	Name: Dr Manpreet Bains Address: C118 Clinical Sciences Building Nottingham City Hospital Hucknall Road Nottingham NG5 1PB Email: manpreet.bains@nottingham.ac.uk

Email: tricia.mckeever@nottingham.ac.uk	
Research Nurse Name: Mrs Norma Thompson Address: Clinical Sciences Building Nottingham City Hospital Hucknall Road Nottingham NG5 1PB Telephone: 0115 823 1315 Email: norma.thompson@nottingham.ac.uk	

Clinical investigation Coordination Centre: Nottingham Respiratory Research Unit,

For general queries, supply of clinical investigation documentation, and collection of data, please contact:

Clinical investigation Coordinator:	Dr Ireti Adejumo
Address:	B35 Clinical Sciences Building, City Hospital, Nottingham.
Telephone:	0115 82 31935
Fax:	
Email:	msxia6@nottingham.ac.uk

Clinical Queries

Clinical queries should be directed to the Chief Investigator, Dr Dominick Shaw, who will direct the query to the appropriate person

Sponsor

Nottingham University Hospitals NHS Trust is the main research sponsor for this clinical investigation. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Nottingham University Hospitals NHS Trust
Research & Innovation, Nottingham Health Science Partners
C Floor, South Block, Queens Medical Centre
Derby Road
Nottingham, NG7 2UH
Email: ResearchSponsor@nuh.nhs.uk

Funder

GlaxoSmithKline (GSK)

This CIP describes the Inhaler Technology Study clinical investigation and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the clinical investigation team. Problems relating to this clinical investigation should be referred, in the first instance, to the Chief Investigator.

This clinical investigation will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the CIP, the Data Protection Act 1998 and other regulatory requirements as appropriate.

AMENDMENT HISTORY

Amendment No.	CIP Version No.	Date Issued	Author(s) of Changes	Details of Changes
1	**1.1**	**21/11/16**	**Ireti Adejumo**	**Inclusion of REC number** **Draft timeline update** **Updates of version number and date**
7 (SA3)	**1.2**	**24/08/17**	**Ireti Adejumo**	**Title page:** **Inclusion of ISRCTN number**
7 (SA3)	**1.2**	**24/08/17**	**Ireti Adejumo**	**Pg 21 (Section 9):** **Correction of oversight (mini-AQLQ included in secondary outcomes)**
7 (SA3)	**1.2**	**24/08/17**	**Ireti Adejumo**	**Pg 23 (Section 10.1);** **Pg 27 (Section 12.3)**

				Recruitment broadened to include respiratory wards, Accident and Emergency and poster display throughout NUH sites.
7 (SA3)	**1.2**	**24/08/17**	**Ireti Adejumo**	**Pg 47 (Appendix 1): Draft study timeline/target dates changed to reflect study start December 2016**
8 (SA4)	**1.3**	**16/10/17**	**Ireti Adejumo**	**Addition of SmartTurbo™ device**
10 (SA5)	**1.4**	**22/03/18**	**Ireti Adejumo**	**Pg 23 (Section 10.1) and Pg 27 (Section 12.3) addition of GP PIC and research sites as sites for consent and study procedures**
10 (SA5)	**1.4**	**22/03/18**	**Ireti Adejumo**	**Pg 26 (Section 11.1) broadening research sites to East Midlands Primary Care CRN**
10 (SA5)	**1.4**	**22/03/18**	**Ireti Adejumo**	**Pg 47 (Appendix 1): Study extension**
10 (SA5)	**1.4**	**22/03/18**	**Ireti Adejumo**	**Reformatting document for Word 2016 and addition of new abbreviations to list.**
11 (SA6)	**1.5**	**09/11/18**	**Ireti Adejumo**	**Pg 23: recruitment broadened**
11 (SA6)	**1.5**	**09/11/18**	**Ireti Adejumo**	**Pg 27: recruitment broadened**

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
CI	Chief Investigator
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRN	**Clinical Research Network**
CT	Clinical Trial
CTA	Clinical Trial Authorisation
EC	Ethics Committee (see REC)
GCP	Good Clinical Practise
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IRB	Independent Review Board
MHRA	Medicinal Health Research Authority
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principle Investigator
PIC	**Participant Identification Centre**
PIS	Participant Information Sheet
R&I	Research & Innovation
REC	Research Ethics Committee
SABA	Short Acting Beta Agonist (s)
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

CLINICAL INVESTIGATION SUMMARY

Clinical Investigation Title	Improving asthma treatment using inhaler technology
Sponsor Reference Number	14RM008
Clinical Phase	4
Clinical investigation Design	2-arm feasibility study using inhaler technology to monitor inhaler use in participants with asthma: A) monitored with no feedback to participants (control); B) monitored with feedback to participants (active);
Clinical investigation Participants	Age 18 to 65 inclusive; physician diagnosis of asthma for at least 12 months; prescribed ICS therapy; on BTS Step 2 to 5 treatment; asthma attack requiring systemic corticosteroids in the previous 12 months
Planned Sample Size	This is a feasibility study of 50 patients (25 each to active and control). We also aim to engage approximately 30 of these patients (15 from active and 15 from control) in qualitative evaluation.
Number of Participants	50 and 30 of these in qualitative interviews.
Follow-up Duration	6 months
Planned Clinical investigation Period	Overall 3 years study duration from approval to include 18 months recruitment and ; 6 months participation per patient
Primary Objective	We will assess whether the use of Inhaler Technology to monitor and feedback on patterns of medication use can improve preventer inhaler adherence and reduce reliever inhaler overuse.
Secondary Objectives	We will assess whether Inhaler Technology is patient friendly and cost effective, aid with asthma treatment decisions, and with the prediction and prevention of asthma exacerbations
Primary End points	Adherence (preventer treatment): The mean percentage of prescribed doses taken daily over the study period i.e. If 2 of 4 prescribed doses taken on day 1, this is 50%; calculate this daily for duration of study period and then average [Sum daily % adherence and divide by number of days of treatment] [as per Foster JACI 2014] Reliever Use: The number of days with >16 actuations/day of Salbutamol taken in a 24-hour period

	Rationale: in a prior study, we used >16 actuations as a threshold of SABA use at which self-management plans recommended medical review [Patel TLRM 2013]
Secondary End points	<u>Improving asthma treatment</u> Studying patient factors for over/under treatment. Assess adherence with standard care asthma treatment. Identify need for stepping up/ down treatment based on inhaler use versus symptoms. Assess capability of technology in real world patients with asthma. <u>Patient feedback and healthcare utilisation</u> Design system of feedback to patients and assess its ease of use, uptake and feasibility. Identify triggers for asthma review and treatment change. Compare costs of Inhaler Technology regime with current costs of routine asthma management. To calculate power needed for design of definitive exacerbation prediction study using this technology
Device Name	SmartTouch™ SmartTurbo™
Manufacturer Name	Smartinhaler™ by Adherium
Principle Intended Use	To monitor inhaler use and send data wirelessly to Smartinhaler™ apps and software.
Length of Time the Device has been Used	Since 2014

FUNDING AND SUPPORT IN KIND

Confidential

INTRODUCTION

Background

The development of new asthma inhalers embedded with technology enabling automated capture of real time data allows us to explore patterns of inhaler use and to relate this to other important factors related with asthma control, rather than relying upon time consuming and laborious measures such as peak flow, questionnaires and prescription counting to determine asthma treatment, symptom control and compliance. New data that can be captured include time of activation and number of activations. When an electronic monitoring inhaler is combined with a smart phone the place of activation can also be obtained allowing other data streams to be collated, including weather, temperature, pollution exposure, traffic exposure, pollen/fungal exposure and patterns of viral infection in the environment.

Recent studies have studied the use of mobile phone-enhanced asthma self-management(246) and the use of inhaler technology-based medication reminders and feedback in primary care asthma patients(68). In both studies, participants were selected on the basis of having poorly-controlled asthma (defined by ACQ or ACT), but approximately two-thirds had mild asthma (Step 0-2(246)) or had not required a course of oral corticosteroids in the prior 12 months(68). In both studies, interventions involved intensive (twice-daily) recording or reminders. Results showed no significant improvements in asthma control compared to the usual-care groups. From these studies, it may be concluded that the application of technology to clinical practice is limited by practicality (need for intensive data collection or feedback) and cost effectiveness (selection of a broad range of participants with predominantly mild asthma, in whom the occurrence of attacks requiring the greatest healthcare resource is relatively uncommon). At present, the evidence suggests that the use of inhaler technology-based feedback may not be cost effective or practical to implement when applied to patients with predominantly mild, poorly controlled asthma. The generalizability of these findings are limited by the use of self-report (rather than electronic monitoring) to measure medication use(246) and the high-intensity reminders and adherence feedback processes(68).

However, adherence to inhaled corticosteroids (ICS) was improved by the use of inhaler technology(68). This suggests that cost-effectiveness may be improved in the sub-group of patients most at risk of healthcare utilisation [patients with prior recent severe exacerbations], if the cost of the use of technology is balanced by a reduction in healthcare utilisation based on severe exacerbations. This may be possible if a link can be demonstrated between improved inhaler adherence using inhaler technology and reduced asthma attacks, in patients at-risk of these events. This is important because it is already well-recognised that poor adherence to asthma treatments commonly occurs in patients with difficult asthma[3]. With the availability of new biological treatments for severe asthma on the horizon, evidence of optimisation of adherence to inhaled therapy in patients with moderate to severe asthma will be crucial prior to prescription of these expensive novel agents. This point is emphasised in a recent editorial[4] of an anti-IL5 Mepoluzimab study[5], in which there was a 50% reduction in severe exacerbations in the placebo group. This is likely partly attributable to improved

adherence to inhalers because of involvement in a clinical trial, illustrating the concept that improvements in inhaler adherence in this at-risk patient group can help to improve asthma outcomes.

The hypothesis is that the use of Inhaler Technology to measure both preventer and reliever medication use and guide patient feedback improves adherence and potentially clinical outcomes (asthma control and exacerbations), and is cost-effective, when used in asthma patients with recent asthma attacks in a practical, real-world setting.

We will recruit 50 patients with mild to severe asthma and issue them with Electronic monitors for both short acting beta agonists (SABA) and inhaled corticosteroids (ICS) and follow them for six months.

We will assess whether this technology is patient friendly and cost effective in three main areas of asthma care; adherence, treatment decisions, and the prediction and prevention of asthma exacerbations. We intend to improve adherence, treatment decision making and patient self-management.

RATIONALE FOR CURRENT STUDY

Adherence

Adherence is a key issue in asthma. Studies have shown that patients over-report use of ICS; one study found that the median use of ICS reported by patients in their diaries was 95%, whereas the median actual use was 58% and more than 90% of patients exaggerated their ICS use[6]. Adherence with ICS therapy is associated with lower mortality rate in asthma[7], whereas reliance on SABAs is associated with increased mortality[8]. The recent National Review of Asthma Deaths (NRAD) report published in May 2014[9] highlighted that on average, 80% of patients who died of asthma over a 1-year period in the UK had been prescribed less than 1 preventer inhaler per month. In addition, this study[9] found that almost 40% of patients who died of asthma had been prescribed more than one reliever inhaler per month.

We will compare prescribed SABA and ICS use with actual treatment use and explore factors for under- and over-use.

Treatment Decisions

In the UK 80% of patients with a diagnosis of asthma are managed solely in primary care where both the diagnosis and decision to increase or decrease treatment is based upon self-reported asthma symptoms. Treatment decisions are made at regular reviews conducted by a nurse or doctor. This system of assessment leaves little flexibility in a highly heterogeneous disease[10], and treatment is often not stepped down quickly or appropriately[11].

We will assess whether electronic inhaler data capture can identify patients requiring more frequent reviews or treatment change and enable proactive self-management.

Exacerbation Prediction

Predicting asthma exacerbations (attacks) is a key goal in asthma research. We will assess whether electronic monitoring technology can be combined with other data sources to build a complete enough picture to begin to understand exacerbation triggers in real-time.

Inhaler Monitoring Device

The Smartinhaler (SmartTouch™/SmartTurbo™) range of electronic monitors will be used to record the use of inhalers by participants in the study. The monitors are manufactured by Adherium Limited, Auckland, New Zealand (http://adherium.com/). Please see the attached product data information sheet provided by the manufacturer for technical specifications Appendix 2. The device will fit around the patient's existing inhaler, and will record the date and time of each actuation. Data is regularly and automatically transferred, via Bluetooth connection, to the Smartinhaler App™ or Smartinhaler Lite App™ on the patient's internet-enabled phone. The phone will be installed with the appropriate app at the first study visit. The app manages the transfer of data. The actuation use data is then transferred from the phone to a secure website-based database, via the internet, using WiFi connection or the internet connection via mobile phone. Investigators can then remotely view and download data from the website.

The devices are compatible with the following MDIs: Fostair® (beclomethasone/formoterol), Seretide® (fluticasone/salmeterol), Ventolin® (salbutamol), Salamol® (salbutamol). They are also compatible with the following Turbohalers: Symbicort® (budesonide/formoterol), Bricanyl® (terbutaline) and Pulmicort® (budesonide).

The manufacturer advises us that the devices are CE marked and for this clinical investigation SmartTouch™/SmartTurbo™ will be used in accordance to their directions for use.

The manufacturer will provide technical support throughout the study. Initial training on the use of the device can be provided by the manufacturer. Dr Shaw and Dr Patel both have experience with the use of this type of electronic monitoring technology from previously-conducted studies.

CLINICAL INVESTIGATION OBJECTIVES

Primary objective

The hypothesis is that the use of electronic monitoring technology to measure both preventer and reliever medication use and to help provide patient feedback improves inhaler adherence and potentially clinical outcomes (asthma control and exacerbations) when used in asthma patients with recent asthma attacks in a practical, real-world setting.

Secondary objective

To assess the utility of electronic monitor-guided care on exacerbation prediction and patient acceptability of use. Cost effectiveness established if scalable from qualitative work. (i.e. barriers to adoption)

ENDPOINTS

Co-Primary endpoints

1. **Preventer use**: The mean percentage of prescribed doses taken daily over the study period
   i.e. If 2 of 4 prescribed doses taken on day 1, this is 50%; calculate this daily for duration of study period and then average [Sum daily % adherence and divide by number of days of treatment](68)

2. **Reliever Use**: The number of days with >16 actuations/day of Salbutamol taken in a 24-hour period.
   Rationale: in a prior study, we used >16 actuations as a threshold of SABA use at which self-management plans recommended medical review[12].

Secondary endpoints

Secondary Outcomes: medication use (Categorised by preventer and reliever medication)

1. Number of days of preventer non-adherence (0 actuations per 24 hours) [expressed as a rate: number of days/days of treatment]
2. Number of days of 100% preventer adherence (when all prescribed doses taken)
3. Mean % of prescribed preventer dose taken daily by month (month 1 to 6)
4. Number of days of overuse of preventer treatment (when more than daily prescribed doses taken i.e. >2 or >4/day) – this is likely to occur in a subset of patients who perceive symptom relief with LABAs and use their combination inhaler for relief or alternatively make up for missed doses
5. Mean daily ICS (preventer) dose (total number of actuations over study period multiplied by dose per actuation) divided by number of days of treatment exposure.
6. Overuse of SABA (reliever): Number of days of >24 and >32 actuations of salbutamol in a 24 hour period
7. Number of days of zero SABA use (reliever)
8. Derive power calculation for full study, based on adherence

Secondary outcomes: clinical control

1. Number of exacerbations (treatment with systemic corticosteroids for asthma or antibiotics)
2. FEV_1 (spirometry)
3. Asthma Control Test (ACT) Score
4. **Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ)**

Secondary outcomes: treatment decisions

1. Patient views/attitudes to monitoring/ feedback*
2. Understand patient factors around using devices*
3. Ease of use/ patient acceptability*
4. Studying the utility of differing thresholds for feedback (e.g. ICS adherence of <75% or <80%; salbutamol thresholds based on number of days of at least one salbutamol actuation or maximal daily number of actuations)
5. Study practicality of data feedback processes
6. Episodes where advice provided to seek GP/clinical review based on monitoring data; and, episodes when participants actually sought review subsequently

* *assessed via interview at final visit.*

CLINICAL INVESTIGATION DESIGN

The study is collaboration between experts in asthma, statistics and human factors and builds upon previous work in this area performed by the investigators. The work will take 3 years, which includes 18 months patient recruitment for a six month study.

Recruitment and Consent

We will initially recruit from our severe asthma service clinic and general respiratory clinics**, respiratory wards, acute admissions wards and Accident and Emergency across** NUH Trust. We will also recruit via the Nottingham Respiratory Research Unit database of research volunteers, and utilising primary care PIC **and research** sites in both Nottingham City and County areas, as well as putting posters up **in public places,** at the University of Nottingham **and around Nottingham University Hospitals NHS Trust**. We will recruit 50 patients at BTS Step 2-5.

Patients aged 18-65 inclusive will be initially approached by a healthcare professional in clinic, or via a letter (if patients have signed up to the NRRU approved database), or through primary care PIC sites (through posters). Potential participants will have the opportunity to read an information sheet and given time before consenting to the study. Current best practice for clinical studies will be followed. Patients must have a doctor diagnosis of asthma for 12 months and be prescribed an inhaled corticosteroid. All patients will require access to their own internet-access enabled mobile phone.

Once recruited, patients will be assessed at the dedicated clinical studies unit within the Nottingham Respiratory Research Unit, **or at their local GP practice where this is a PIC or research site,** at a time convenient to the patient. A brief clinical history will be taken. Asthma control will be assessed by Asthma Control Test (ACT) questionnaire and treatment continued as per current guidelines. Asthma Quality of Life will be measured by the mini Asthma Quality of Life Questionnaire (mini AQLQ). Spirometry with reversibility will be undertaken according to a standardised protocol. Baseline data on asthma phenotype will be collected from the patient's medical record where available (e.g. prior eosinophilia, Skin prick test results, exhaled nitric oxide, IgE). Randomisation will occur and the electronic monitors will then be fitted to the inhaler. Inhaler technique will be checked and patients issued with contact details for the study team.

Patients will be allocated to one of two groups in order to study the effects of being monitored and having feedback. Establishing these differential effects will be crucial in understanding any future impact of Inhaler Technology. The groups will be as follows:

Group A: (control) a monitored group where patients have their dosing monitored but have no feedback on inhaler usage

Group B: (active) a feedback group where inhaler usage is openly monitored, and with specific feedback about usage patterns with the results provided to the patients.

Group A

In the control group, participants will be informed that they have been provided an inhaler that can measure medication use over the study period and allow this information to be studied alongside symptoms as measured by ACT. In order to obtain medication use data in an unbiased format, participants will not be told that their inhalers can record patterns of medication use. The Smartinhaler Lite™ smartphone application which they will have installed will not provide access to their own adherence data.

This method involves minimal risk to the patient, because we are just recording/observing current usual inhaler use. Because treatment use may be affected by knowledge of being monitored, this method benefits from allowing the most accurate method to measure medication use in the control group. In prior similar situations where the (minimal) risk of covert monitoring has been outweighed by the benefit of unbiased data collection, ethics approval has been obtained [Foster JACI 2014[2], page e1, 'Electronic inhaler monitoring': patients in the control group were told that the monitors were to 'help keep track of patient's asthma control' and the monitors were not labelled by their commercial name]. At the final study visit, patients will be informed of the recording capabilities of the monitors, provided with a summary of their adherence data and have the opportunity to discuss this with a member of the study team. Please see further details on consenting participants in Section 12.4.

Group B

In the active group, feedback will be given by an investigator (research nurse or PhD student) via a phone call every 4 weeks if adherence is outside pre-set thresholds based on the results of the inhaler tracking over the prior study month. The phone call will include a discussion of adherence data, and advice to contact the patient's GP/nurse in the setting of worsening asthma. The format below will be used as a guide during feedback:

- 'Your preventer inhaler has been used for less than half the recommended number of doses over the past 4 weeks. This could lead to your asthma getting worse or not being as well controlled as possible.' **And/or**

- 'Your reliever inhaler has been used often during at least one week recently. This could mean that you asthma is not being as well controlled as possible'.

A copy of the adherence data will be sent to the GP if clinical review is suggested.

Patients will also be able to view their own adherence data via the Smartinhaler App™.

Study Visits

All Patients will be seen at visit 1 (week 0, baseline) and at visit 7 (week 24, end of study), giving a total of 2 visits to site per patient.

All patients will complete follow-up questionnaires every 4 weeks i.e. Visit 2-6 (Weeks - 4,8,12, and 20) remotely (e.g. by telephone call, email, or online web-based survey). Questionnaires will include the ACT and mini AQLQ and questions on changes to treatment will be asked. If a participant does not return the questionnaire data, then they will be contacted via phone/text/email to remind them to complete this.

All patients will be advised to seek help from their GP if they suffer from poor control. In the event of an asthma emergency, patients will seek urgent care as per usual, via 999, the GP or Emergency Department.

CLINICAL INVESTIGATION POPULATION

Number of Participants

50 participants, site**s** Nottingham Respiratory Research Unit **and East Midlands primary care CRN**, **24** months recruitment time for a 6 month person follow-up time.

Inclusion Criteria

- Age18-65 inclusive
- Use of systemic corticosteroids for worsening asthma (or an increase from baseline dose in patients on long-term oral corticosteroids) in the prior 12 months [i.e. at least one asthma exacerbation requiring additional systemic corticosteroid in the prior 12 months] patient reported.
- Doctor's diagnosis of asthma for at least 12 months
- On BTS step 2-5 treatment via MDI [monitoring devices to be utilised in the study are compatible with MDI inhalers]
- Use of own internet-enabled and compatible mobile phone

- Participant is willing and able to give informed consent for participation in the clinical investigation.
- Able (in the Investigators opinion) and willing to comply with all clinical investigation requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the clinical investigation.

Exclusion Criteria

- Diagnosis of COPD or onset of symptoms after the age of 40 in patients with ≥10 Pack Year History of smoking
- Other clinically significant coexisting respiratory disease e.g. fibrosis, bronchiectasis
- No personal mobile smartphone
- Patients on maintenance and reliever therapy ('SMART' or 'Fostair® MART')
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the clinical investigation, or may influence the result of the clinical investigation, or the participant's ability to participate in the clinical investigation.

PARTICIPANT SELECTION AND ENROLMENT

SCREENING FOR ELIGIBLE PARTICIPANTS

Demographics

The date of birth, gender, smoking and asthma and clinical history in keeping with the inclusion/exclusion criteria will be recorded.

Medical History

Details of any history of disease or surgical interventions in the following systems will be recorded: asthma and general medical.

Concomitant Medication

All prescription medication will be recorded.

Trial / study configuration

Single centre study, but GP practices may act as Patient Identification Centre sites as they may display a poster advertising the study as will the University of Nottingham campus.

Recruitment

The study will be conducted by the Nottingham Respiratory Research Unit at Nottingham City Hospital. Patients will be recruited from clinics, existing volunteer databases, **NUH (and specifically respiratory wards and Accident and Emergency)** and primary care PIC **and research** sites or University of Nottingham. **Recruitment posters will be displayed in public places.** Visits will be conducted at the Respiratory Research Unit **or at participating primary care PIC and Research sites**.

Consenting Participants

General

The participant must personally sign and date the latest approved version of the informed consent form before any study procedures are performed.
Written participant information sheets and Informed consent forms will be presented to the participants detailing no less than: the exact nature of the clinical investigation; the implications and constraints of the clinical investigation plan; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the clinical investigation. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be

suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent and accompanying participant information sheet will be given to the participants and a copy filed in the medical notes. The original signed form will be retained within the Investigator Site File.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms. If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for on-going participants).

Specific

To obtain objective medication use data in the control group (Group A), participants will not be told of the exact capabilities of the monitor to record patterns of medication use. This approach has received ethical approval previously(68). The process of consent will follow the published guidance about blinding of device studies and ethics for randomised trials of non-pharmacological interventions, as per Boutron et al[13]:
'Blinding participants to study hypotheses could also be proposed when the comparator is an active control treatment of the same nature or different nature by use of a modified Zelen design. Such design is a two-stage procedure, in which patients are asked to provide consent for an observational study in the first stage. Then patients are randomized to the experimental treatment and the control arm, and in the second stage are asked to provide a second consent for treatment.'

The process will be as follows:

1. Potentially eligible participants will be informed that the study is investigating the use of technology in asthma and that this involves use of an inhaler that will 'help keep track of asthma control'(68). Participants will be blinded to detailed study hypotheses and outcomes.
2. Eligible patients will be consented and then randomised.
3. Patients randomised to the control group will continue as per Group A; patients randomised to groups B will be provided further information about the active arm and will then be asked to sign an additional consent form.

The NPSA has provided guidance on the practice of withholding information in medical research (http://www.hra.nhs.uk/documents/2013/09/ige-paper-deception-in-medical-research.pdf). Withholding information may be permissible if:

1. 'no other research method would suffice'
2. The subject is not exposed to anything other than 'minimal risk'
3. Debriefing occurs at the end of the study
4. The rationale for the planned withholding of information is clearly justified and supported by scientific expert review.
5. This study meets the above requirements.

Randomisation and Blinding

This is an open label trial. Randomisation will be via a computer generated sequence..

Study Processes

Feedback of medication use

ICS low-adherence: Low adherence defined as more than 14 days (i.e. 15 days or more) [over the preceding 4 weeks] on which there was less than 50% ICS adherence per day [Suissa NEJM[7]: 'The rate of death from asthma among users of inhaled corticosteroids as compared with nonusers was reduced by about 50% with the use of more than six canisters per year i.e. >6 canisters over 12 months, >50% adherence].

Reliever use: ≥ average 6 actuations of salbutamol per day during any one week over the preceding 4 weeks [i.e. categorise the preceding 1 month into 4 one-week windows and calculate the average daily salbutamol use for each of these 4 windows]. Average daily salbutamol use is a significant predictor for future severe asthma exacerbations[14]. In comparison to a patient with no salbutamol use over 2 weeks, a patient using an average of six inhalations of salbutamol per day has twice the odds for a severe asthma exacerbation in the next 6 months[14]. 6 inhalations of salbutamol per day equates to approximately one canister of salbutamol per month, which is associated with twice the odds of death or near death compared to no salbutamol use[15].

ACT scores will be collected but this data will not be used to determine feedback calls. This information will be analysed as an outcome of the study to determine the relationship between ACT score, medication use and feedback options.

Qualitative data
Research methods will include surveys and interviews with patients.

Semi-structured interviews will be arranged at the end of the 6 month period with the sub-sample of patients who provided consent to take part at the point of recruitment. Approximately 30 patients will be interviewed (15 active, 15 control). Should more patients provide consent than required, we will purposively sample patients to ensure varying levels of adherence (both observed and subjective as measured by an adherence questionnaire such as the Medical Adherence Report Scale – Asthma or 'MARS-A') and varying ACT scores are included.

Semi-structured interviews will be conducted either face-to-face or via telephone. To minimise study burden, we will strive to coincide face-to-face interviews with the final visit.

The semi-structured interview guide will explore patients' views of the device, including the ease of use, social acceptance, portability, practicality and aesthetics. The guide will cover topics around what patients thought about being monitored, data sharing and communication and feedback related to the monitoring. It will also ask about how views on being 'tracked via GPS' for future projects. Finally, the guide will also consider areas for improvement, particularly with regards to how the device, communication and feedback could be improved to increase patient engagement.

We will continue to recruit until we reach saturation of new opinions and themes being generated from each group of patients.

Qualitative Data Analysis

Interviews will be digitally audio-recorded and transcribed verbatim. This will be carried out, in the first instance, by the PhD student under the supervision of Dr Manpreet Bains (associate professor of health research University of Nottingham). A proportion may also be carried out by a university approved external transcription service. Data will be stored and managed using NVivo® software. Following receipt of the transcripts, the researchers will ensure all personal identifiers are removed and that transcripts are accurate. Participants will be assigned a code that will only identify the group they represent (active, control). Data generated from the interviews will then be analysed (by the PhD student and Dr Manpreet Bains) using the framework approach[17] which is a hierarchical, matrix based method developed for applied or policy-relevant research which allows focused interrogation of data. The framework approach will allow the research team to map whether there are differences/similarities according to the individuals sampled (active, control, adherence level). Data will be coded using inductive approaches, where the familiarisation stage will enable the identification of themes and sub-themes. Data will then be indexed according to the identified themes and sub-themes. Themes and sub-themes will then be discussed between the research team, which will allow clarification of the final framework. Using NVivo® software, data will then be charted according to each theme to synthesise the data and aid interpretation. Extracts from interviews will be included in the charts.

Study outcome measures

Patients will have 6 months follow-up in the study. For all patients, individual feedback regarding patterns of medication use will be provided in summary format at study completion, with an opportunity to discuss with the study research nurse or PhD student.

Participant reimbursement

£20 (total) per participant will be provided to cover the cost of data charges/text messages/phone calls, and for travel.

Withdrawal of Participants

Any patient is able to withdraw from the study at any point. For patients who withdraw prior to study completion, a final close-out visit will be requested with the patient. The data collected so far will still be used in the final analysis of the study. Participants who lose mental capacity during the study will be withdrawn, but their data collected up to that point will still be used.

MEDICAL DEVICE

DEVICE DETAILS

SmartTouch™, CE Marked
SmartTurbo™, CE Marked

DEVICE MANUFACTURER

Adherium, Suites 205-206, 8 Commerce Street, Auckland 1010, New Zealand

MARKETING AUTHORISATION HOLDER
Adherium, Suites 205-206, 8 Commerce Street, Auckland 1010, New Zealand

Device Accountability

Inhaled medication for asthma

Patients will continue on their usual prescribed inhaled preventer and reliever medication. Electronic monitoring of MDI use has an established track record in clinical studies[2,16]. Monitoring of use of other inhaler devices is less well established. Patients who use MDI inhalers only will therefore be recruited. Patients will obtain replacement inhalers from their usual primary/secondary care doctors. At the first visit, patients will be shown how to fit the monitoring device to their inhaler and will be provided with information regarding this and care of the monitor. Patients will transfer their electronic monitor onto any new inhalers during the trial. Patients will be offered telephone support at any point during the study for monitor problems, including but not restricted to, problems with transfer onto new inhalers, damage, loss, malfunction. For monitors that are lost, replacements will be provided and this will be recorded as an outcome for the study. Patients will be provided several electronic monitors each to account for multiple inhalers. If a patient's inhaled therapy changes during study participation (for instance, due to a step-up in therapy), this data will be recorded at the 4 weekly data collection via phone/text/email.

Electronic Monitor Quality Control Process

All monitors will be tested pre commencement of study for correct functioning prior to being used in the trial and will undergo a within-trial Quality Control process, in keeping with prior recommendations[16].

Malfunctioning monitors will be replaced and a process will be implemented whereby these monitors will be returned to the manufacturer for attempted data extraction and fault analysis.

CLINICAL INVESTIGATION ASSESSMENTS

Visit number	0	1	2-6	7
Visit type	Run in	Site visit	Telephone call	Site visit
weeks		0 (baseline)	4,8,12,16, 20	Week 24 (EOS)
Information sheet given	X			
Information sheet discussed	X	X		
Informed consent		X		
Determine eligibility		X		
Randomisation		X		
Medical / asthma History		X		
ACT, mini AQLQ		X	X	X
Spirometry and reversibility		X		X
Fit electronic monitors		X		
Check inhaler technique		X		
Review written asthma plan (if already in place)/provide plan		X		
Provide information on electronic monitors		X		
Discuss feedback methods depending on group		X		
Letter to GP		X	X (a)	X
Download data from monitors			X	X
Collect self-reported data on asthma exacerbations, change in asthma treatment, scheduled or unscheduled healthcare visits for asthma			X	X
Self-reported Adverse Event and Serious Adverse Event data [respiratory events]			X	X
Review of adherence data, debriefing to all groups and letter to GP				X
Perform semi-structured interview with selected participants				X
Adherence questionnaire e.g. MARS-A (b)				X

(a) If applicable: see section 10.1 – applies only to active monitoring group (Group B)
(b) See section 12.6 – participants consented for semi-structured interview only to aid sampling

DATA COLLECTION

Source documents are original documents, data, and records from which participants' Case Report Form data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this clinical investigation the CRF will be used as the source document for all study information required and collected.

All documents will be stored safely in confidential conditions. On all clinical investigation-specific documents, other than the signed consent, the participant will be referred to by the clinical investigation participant number/code, not by name.

STATISTICS

Description of Statistical Methods

This is a feasibility study and is planned to help inform the potential conduct a future larger definitive trial.

Statistics: This is a feasibility study. For the primary outcome, a non-parametric distribution is anticipated. Appropriate non-parametric tests, such as the Mann Whitney test, will be used. Mixed-model analysis will be used to examine patterns of change with time. Health economic analysis will be performed.

THE NUMBER OF PARTICIPANTS
50

THE LEVEL OF STATISTICAL SIGNIFICANCE
$P<0.05$

PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED AND SPURIOUS DATA
The quality control processes detailed above should minimise the quantity of missing or spurious data. Please see p.34 under Medical Devices section for details.

PROCEDURES FOR REPORTING ANY DEVIATIONS(S) FROM THE ORIGINAL STATISTICAL PLAN
To be reported in the final report. Any deviations from the Statistical Analysis Plan will be documented within the Trial Master File and will be reported in the final report, along with the justification for these deviations.

INCLUSION IN ANALYSIS
All randomised participants will be included within the analysis.

SAFETY REPORTING

Definitions

Adverse Event (AE)

An AE or adverse event is:
Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a clinical investigation of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

Adverse Device Effect (ADE)

All untoward and unintended responses to the medical device.
The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Event (SAE)

SAE is an adverse event that

- Led to death
- Led to foetal distress, foetal death or congenital abnormality or birth defect.
- Led to serious deterioration in the health of the subject that:
    - Resulted in a life-threatening illness or injury
        - NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
    - Resulted in a permanent impairment of a body structure or a body function
    - Required in-patient hospitalisation or prolongation of existing hospitalisation
    - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
    - Other important medical events*
        - *Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Device Effects (SADE)

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to characteristics of a serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances have been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

Reporting of AEs

All AEs occurring during the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the clinical investigation plan. All ADEs will be recorded in the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.

All ADE that result in a participant’s withdrawal from the clinical investigation or are present at the end of the clinical investigation, should be followed up until a satisfactory resolution occurs.

AE data relating to respiratory events/conditions will be collected at scheduled patient visits/contacts via participant self-report and by using standard questions: ‘Have you had any asthma or breathing-related problems since the last contact?’; ‘Is there anything new about your asthma or breathing that you wish to discuss?’

ADE data will be collected at scheduled patient visits/contacts via participant self-report and by using standard questions: 'Have you had any problems with the inhaler device?'

Reporting Procedures for all SAEs/ SADEs/ USADEs

For studies of CE marked devices:
All SAE/SADE/USADEs will be reported to the sponsor/legal representative and manufacture and NUH R&I **within one working day** of the investigator team becoming aware of them.

All SAEs must be reported to R&I within one working day of discovery or notification of the event.
Reporting to the MHRA, where required, will be done in liaison with the Chief Investigator and the Manufacturer.

The Manufacturer has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) after a link is established between the event and the device, but no more than:

- 2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

Annual Reports

In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical investigation or on request a Safety Report to R&I, and the Research Ethics Committee.

CLINICAL INVESTIGATION MANAGEMENT

Clinical Investigation Management Group

The following group will meet monthly to monitor progress of study.
Dominick Shaw – Chief Investigator
Mitesh Patel – co-investigator
Research Nursing Team – screening, consent, patient visits, follow-up
PhD student - screening, consent, patient visits, follow-up

Inspection of Records

Investigators and institutions involved in the clinical investigation will permit clinical investigation related monitoring and audits on behalf of the sponsor and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all clinical investigation records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all clinical investigation records and source documentation

Risk Assessment

A risk assessment will be performed by the Sponsor to determine if monitoring is required and if so, at what level.

Clinical Investigation Monitoring

A Research Project Manager from Nottingham University Hospitals will visit the Investigator site prior to the start of the clinical investigation and during the course of the clinical investigation if required, in accordance with the monitoring plan. Monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the clinical investigation plan and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the clinical investigation plan, GCP and the applicable regulatory requirements.

GOOD CLINICAL PRACTICE

DECLARATION OF HELSINKI
The Investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

ICH GUIDELINES FOR GCP
The Investigator will ensure that this clinical investigation is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

APPROVALS
The clinical investigation plan, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), the Health Research Authority (HRA) and host institution(s) for written approval, where necessary.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

PARTICIPANT CONFIDENTIALITY
The clinical investigation staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any

electronic database. All documents will be stored securely and only accessible by clinical investigation staff and authorised personnel. The clinical investigation will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Data Handling and Record Keeping

The participants will be identified by a clinical investigation specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any clinical investigation data electronic file.
Interview data will be held on audio interview files and documents showing the transcribed recordings. A hard copy of data from the interviews will be kept securely in a locked filing cabinet within Clinical Sciences Building (University of Nottingham) for a period determined by the sponsor. Electronic files (including audio files) will be held securely on password protected computers within the Clinical Sciences Building, accessible only to the research team.

CLINICAL INVESTIGATION CONDUCT RESPONSIBILITITES

Clinical Investigation Plan Amendments

Amendments to the clinical investigation plan must be submitted to the Sponsor for review before submitting to the appropriate REC, HRA and local R&I for approval.

Clinical Investigation Plan Violations, Deviations and Serious Breaches

The CI will not implement any deviation from the clinical investigation plan without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to clinical investigation participants.

In the event that the CI needs to deviate from the clinical investigation plan, the nature of and reasons for the deviation will be recorded in the CRF and notified to the Sponsor using the appropriate Deviation Form according to NUH SOP-RES-017. If this necessitates a subsequent clinical investigation plan amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Health Research Authority and local NHS R&I for review and approvals as appropriate. It is Sponsor policy that waivers to the clinical investigation plan will not be approved.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately. Refer to SOP-RES-017 “Non-Compliance and Serious Breach Reporting”.

Clinical Investigation Record Retention

All clinical investigation documentation will be kept for 10 years from the clinical investigation plan defined end of clinical investigation point. When the minimum retention period has elapsed, clinical investigation documentation will not be destroyed without permission from the sponsor.

End of Clinical Investigation

The end of clinical investigation is defined as the last participant's last visit.
The Investigators and/or the clinical investigation steering committee and/or the co-sponsor(s) have the right at any time to terminate the clinical investigation for clinical or administrative reasons.

The end of the clinical investigation will be reported to the REC within 90 days, or 15 days if the clinical investigation is terminated prematurely. The Investigators will inform participants of the premature clinical investigation closure and ensure that the appropriate follow up is arranged for all participants involved.

A summary report of the clinical investigation will be provided to the REC within 1 year of the end of the clinical investigation.

Insurance and Indemnity

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical investigation as a result of negligence on the part of a member of the clinical investigation team this liability cover would apply.
Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

Funding

GSK have provided funding for the study.

REPORTING, PUBLICATIONS AND NOTIFICATIONS OF RESULTS

Authorship Policy

Ownership of the data arising from this clinical investigation resides with the sponsor, Nottingham University Hospitals. On completion of the clinical investigation, the clinical investigation data will be analysed and tabulated, and a clinical investigation report will be prepared in accordance with ICH guidelines.

Publication

The report will be submitted to a peer-reviewed journal.

PEER REVIEW

This study has been peer reviewed by experts from:

University of Nottingham (Professor of Epidemiology)

Imperial College Hospital, London. External / Independent (Associate Professor of Child Health)

REFERENCES

1. Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D, et al. Clinical and cost effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. *BMJ* 2012;344:e1756.
2. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014; 134(6): 1260-8.
3. Heaney LG, Horne R. Non-adherence in difficult asthma: time to take it seriously. *Thorax* 2012; 67(3): 268-70.
4. Nair P. Anti–Interleukin-5 Monoclonal Antibody to Treat Severe Eosinophilic Asthma. *N Engl J Med* 2014;371(13):1249-51.
5. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *N Engl J Med* 2014;371(13):1198-207.
6. Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Noncompliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996;98(6 Pt 1):1051-7.
7. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343(5):332-6.
8. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):604-10.
9. Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. London: RCP, 2014. Available at: https://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf
10. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218-24.

11. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326(7399):1115.
12. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013;1(1):32-42.
13. Boutron I, Guittet L, Estellat C, Moher D, Hrobjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med* 2007;4(2):e61 doi:10.1371/journal.pmed.0040061
14. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A, Helm C, et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. *Clin Exp Allergy* 2013;43(10):1144-51.
15. Spitzer W, Suissa S, Ernst P, Horwitz R, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326(8):501-6.
16. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol In practice* 2013;1(1):83-91.

17. Ritchie J LJ. Qualitative Research Practice: A guide for social science students and researchers. London.: Sage.; 2003.

APPENDICES

Appendix 1 - DRAFT CLINICAL INVESTIGATION TIMELINE

Milestone	**Target Date**
Final Protocol Approved	August 2016 (0m)
Ethics Committee submission (HRA Submission)	August 2016
Ethics Committee Approval (HRA Approval)	~~**September 2016**~~ **December 2016**
First Subject, First Visit	~~**October 2016 (3m)**~~ **December 2016 (4m)**
Last Subject, First Visit	~~**April 2018 (21m)**~~ ~~**June 2018 (22m)**~~ **December 2018 (28m)**

Last Subject, Last Visit	~~**September 2018 (26m)**~~ ~~**December 2018 (28m)**~~ **June 2019 (34m)**
Database Freeze	~~**December 2018 (29m)**~~ ~~**April 2019 (32m)**~~ **August 2019 (36m)**
Final Report delivered to GSK	~~**July 2019 (36m)**~~ ~~**August 2019 (36m)**~~ **October 2019 (38m)**

Appendix 2 – MEDICAL DEVICE/SOFTWARE PRODUCT INFORMATION

Confidential

Appendix D: Patient information and consent

Participant Information Sheet (MAIN)

Version: 2.3 Date: 11th June 2018

Study Title: Improving asthma treatment using inhaler technology

Principal Investigator: Dr Dominick Shaw

PART 1

1. Invitation

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully, and discuss it with friends or family if you wish.

PART 1 tells you the purpose of this study and what will happen to you if you take part.

PART 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the purpose of the study?

Although we aim to keep asthma symptoms controlled, lung function at its best and to reduce adverse effects from medicines, these aims are not always achievable. One way to better understand why this happens is by using inhalers that can record information about your asthma.

Our aim is to involve 50 patients, all of whom have had at least one asthma attack in the past year. Each patient will be involved for 6 months and will be asked questions about their asthma. There are only 2 planned visits, either to the Nottingham Respiratory Research Unit or to your GP surgery if this has been agreed; one at the start and one at the end of the study. During the rest of the 6 months, the study team will keep in touch with you by phone, email or text message. The study is based at Nottingham University Hospitals NHS Trust.

3. Why have I been chosen?

You have been chosen because you have been diagnosed with asthma, are prescribed a preventer (steroid) inhaler for your asthma, and have had at least one asthma attack in the past year where you have needed tablet steroids (or more than your usual dose if you already take tablet steroids every day). You will also already be using a mobile phone that can connect to the Internet (for example, to check your email or to use Facebook).

4. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form to confirm that you understand what is involved when taking part in this study. If you decide to take part you are free to leave the study at any time and without giving a reason. If you withdraw, unless you object, we will still keep records relating to the treatment given to you, as this is valuable to the study. A decision to withdraw at any time, or a decision not to take part, will not affect the quality of care you receive

5. What will happen to me if I take part?

If after reading this information sheet and talking to a member of the research team, you would like to take part in this study, you will be seen at Nottingham City Hospital in the Nottingham Research Respiratory Unit (or

at your GP surgery if this has been agreed) and asked to sign a consent form to give us permission to involve you in the study.
This first visit takes about 1 hour and the following will take place:

a. **Information about your asthma**: we will ask you about your asthma history and also look at your medical records from the hospital and your GP (where possible) to get as much information about your asthma as possible
b. **Questionnaires**: you will fill out questionnaires on your current asthma symptoms (every 4 weeks) and your medications
c. **Spirometry**: we will measure the amount of air that you can breathe out. You will be asked to blow as hard as you can into a tube which is connected to a recording device and repeat this several times. We will then give you 4 puffs of salbutamol, wait 15 minutes and ask you to repeat the test. You may have to withhold some of your usual inhalers a few hours before this test, but we will let you know in advance (you may have done this test before at your GP practice).
d. **New inhalers casings provided**: To allow us to collect information about your asthma, you will be provided with new inhaler casings that clip around your current preventer and reliever inhalers. The casings help tell us how well controlled your asthma is. The casings link up to your mobile phone and send this information back to us via the internet. We will show you how to swap over the casings onto your new inhalers that you use during the study.
e. **Inhaler technique and asthma action plan**: we will provide you with a written asthma action plan and check your inhaler technique.

Your participation in the study lasts for 6 months. After this first visit, you will complete a questionnaire about your asthma, and the new casings once every month and we will contact you (by text, email or phone) to remind you if needed. Otherwise, you can go about your daily life as usual. We will make

an appointment to see you at Nottingham City Hospital or at your GP surgery at the end of the study. This final visit will take about 1 hour. We will measure your spirometry (as above), find out how your asthma has been over the past 6 months and collect your inhaler casings. We will also discuss how you felt about using the new casings.

You may also be asked at the end of the study if you would like to take part in an interview with one of our research team, where you will be asked about your experience in the trial. This conversation will be audio recorded so the research team can concentrate on what you are saying without having to take notes. Interviews will then be transcribed anonymously. Anonymised quotes from these transcriptions may be used publications generated from this study.
We will give you contact details for our research team in case you have any questions over the 6 months.

6. What do I have to do?

You should carry on as normal; this study should not affect your lifestyle and you should continue to take your normal medication as per usual.

The day-to-day care of your asthma with remain in the hands of your General Practitioner (GP). If during the study you have an asthma attack, you should go to see your GP, or go to an out-of-hours clinic/call 111 or the hospital emergency department (ED) and seek medical care - you will receive the same care and treatment as you would do if you were not involved in the study. Your asthma action plan will also provide you with guidance as to when to seek help or start a course of tablet steroids for your asthma

7. What is the drug / treatment that is being tested?

We are not testing any drugs in this study – you will continue to use your usual current inhaled preventer and reliever asthma treatments.

8. **What are the alternatives for diagnosis or treatment?**

If you choose not to take part in the study, your care will not be affected and you will continue to be treated as per usual.

9. **What are other possible disadvantages and risks of taking part?**

Performing spirometry can make you feel light-headed and short of breath, but the test is generally very safe.

If you do decide to take part in the study, you must report any problems you have to your study nurse or doctor. There is also a contact number given at the end of this information sheet for you to phone if you become worried at any time. In the unlikely event of an emergency occurring during the conduct of the study, we may contact your nominated next of kin.

If you notice any problems with the inhaler casings or if any become lost, we will give you contact details for our team so that we can repair/replace them.

10. **What are the possible benefits of taking part?**

We cannot promise the study will help you, but it is hoped that we will be able to learn about asthma attacks and medication use. This will allow us to better understand and plan future care for people with asthma.

11. **What happens when the research study stops?**

We will review your progress in the 6 months of the study with you at your final study visit. We intend to publish the results in a scientific respiratory journal. A summary of the results will be available to you should you wish. The device is for research purposes only at present and will therefore not be available to you after the study has finished.

12. **What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and wish to complain formally, you can do this

through the NHS Complaints Procedure. Details can be obtained from the hospital or you can contact PALS (Patient Advice and Liaison Service) telephone 0800 183 0204.

In the unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

13. **Will travel expenses and phone data charges be reimbursed?**

Yes, mileage/travel allowance will be available. You will also receive an allowance for phone data charges (maximum £20 allowance overall for 6 months).

14. **Will my taking part in this study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. Details are included in Part 2.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

15. **What if new information becomes available?**

Sometimes during the course of a clinical trial, new information becomes available. If this
happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make

arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

16. **What will happen if I don't want to carry on with the study**?

You can withdraw from the study at any time but we will use the data collected up to your withdrawal. We will also need to collect the inhaler casings that we have provided you.

17. **Will my part in this study be kept confidential?**

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital and at Nottingham University Hospitals NHS Trust under the provisions of the General Data Protection Regulation. Your name will not be passed to anyone else outside the research team or the sponsor, who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms.

If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis.

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Research Sponsor, which is the organisation responsible for ensuring that the study is

carried out correctly. A copy of your consent form may be sent to the Research Sponsor during the course of the study. By signing the consent form you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority and Independent Ethics Committee; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant.

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 15 years. Arrangements for confidential destruction will then be made.

With your permission on the Consent form, your GP (and other doctors who may be treating you) will be notified that you are taking part in this study.

18. **Use of your personal data in research**

Nottingham University Hospitals NHS Trust is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Nottingham University Hospitals NHS Trust will keep identifiable information about you until study closure.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information www.nuh.nhs.uk.

Nottingham Respiratory Research Unit (NRRU, which is a part of Nottingham University Hospitals NHS Trust) and the East Midlands Primary Care Network (PCRN) will collect information from you and/or your medical records for this research study in accordance with our instructions.

Nottingham Respiratory Research Unit and the East Midlands PCRN will use your name, date of birth, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Nottingham University Hospitals NHS Trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The NRRU and East Midlands PCRN will pass these details to Nottingham University Hospitals NHS Trust (the study Sponsor) along with the information collected from you and/or your medical records. The only people in Nottingham University Hospitals NHS Trust who will have access to information that identifies you will be people who need to contact you for the purpose of study oversight or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

The NRRU and East Midlands PCRN will keep identifiable information about you from this study until study closure.

Data collected during the study may be transferred for the purpose of processing, analysis, etc to associated researchers within/outside the European Economic Area. All data transferred out of the UK/EU is protected under GDPR.

Your asthma control data will be stored on a password-protected website. The website will not contain any identifiable information about you and will use a code that is only known to researchers.

If you are willing to participate in the final interview, anonymous quotes taken from this interview may be published. Neither the transcriptions of this interview nor any of these quotes will contain any identifiable information about you.

19. **Informing your General Practitioner (GP)**

With your permission on the Consent Form, your GP (and other doctors who may be treating you) will be notified that you are taking part in this study. Your GP (and other doctors who may be treating you) will also be provided information on your progress at the end of the study.

If you take a course of steroids for your asthma, either in tablet or liquid form or into your veins in hospital, then we would like you to make a note of the date this treatment started together with how many days you were treated for; you will be asked about this at each study vists This is so that we can keep a record of when your asthma has been troublesome. We will ask for your permission on the Consent Form to obtain further information about your health from the hospital or GP records. To make sure that we have all the information we need about the attack, we will need to contact the health service provider involved to check the medical details.

20. **What will happen to any samples I give?**

We are not taking any samples.

21. **Will any Genetic testing be done?**

No.

22. **What will happen to the results of this clinical trial?**

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor.

23. **Who is organising and funding this clinical trial?**

The Nottingham University Hospitals NHS Trust will act a sponsor the research. GlaxoSmithKline has provided funding for the study.

24. **Who has reviewed the study?**

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and given a favourable opinion by the NHS by London Central Research Ethics Committee.

The study has also been reviewed and approved by the Research & Innovation department of Nottingham University Hospitals NHS Trust.

25. **Contact for further information**

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the intervention involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact one of the following people: at the end of this information sheet.

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

26. Contact Details

Doctor

Name Dr Ireti Adejumo

Tel. Number: 0115 82 31935

Research/Specialist Nurses

Name Mrs Norma Thompson

Tel. Number: 0115 82 31315

07967327318

Name: Miss Clair Parrish

Tel. Number:

Nottingham Respiratory Research Unit

• Asthma • COPD • ILD • Lung Infection •

Participant Information Sheet (Group B)

Version: 2.3 Date: 11th June 2018

Study Title: Improving asthma treatment using inhaler technology

Principal Investigator: Dr Dominick Shaw

You are receiving this information sheet because you have previously consented to take part in the study "Improving asthma treatment using inhaler technology". Participation in this study involves randomisation into one of two groups: This randomisation was done by a computer, equivalent to picking names out of a hat.

You have been randomly selected to be in the Group B

Group B

This means that every 4 weeks the researcher will contact you by phone, email or text message to give you feedback on your medication use, which is measured via the inhaler casings. You will also get feedback on how well your asthma is controlled. The Researcher may advise you to seek care from your GP if your asthma is not well-controlled.

Please refer back to the previous information sheet you were provided (Version 2.3 dated 11th June 2018) as well as the information provided in this sheet to inform your decision of whether or not you want to continue to take part in the study.

If you any further questions please speak to the researcher or research nurse.

If you decide you would like to take part then please read and sign the second consent form.

Contact Details

Doctor:

Dr Ireti Adejumo Tel. Number: 0115 82 31935

Research/Specialist Nurses:

Mrs Norma Thompson Tel. Number: 0115 82 31315

Miss Clair Parrish Tel. Number: 07967327318

I'm interested and would like to know more…

If you would like to get involved in this study, please contact the study team using the information below.

We will ask a few questions to confirm your suitability, send you a full information sheet and arrange an appointment for you to come in.

Contact Details

Ireti Adejumo 0115 823 1935

Norma Thompson 0115 823 1315

Clair Parrish 07967327318

Email: msxia6@nottingham.ac.uk

Nottingham Respiratory Research Unit
• Asthma • COPD • ILD • Lung Infection •

IRAS 193750
REC 16/LO/1693
Patient Information Summary Version 1.1 11/06/18

Nottingham Respiratory Research Unit
• Asthma • COPD • ILD • Lung Infection •

IRAS 193750
REC 16/LO/1693
Patient Information Summary Version 1.1 11/06/18

Nottingham University Hospitals NHS
NHS Trust

Patient Information Summary

Study Title:	Improving asthma treatment using inhaler technology
Chief Investigator:	Dr Dominick Shaw
Other researchers:	Dr Ireti Adejumo Mrs Norma Thompson Mr Mohammad Ali Miss Clair Parrish

Nottingham Respiratory Research Unit
• Asthma • COPD • ILD • Lung Infection •

Tel: 0115 823 1935/ 0115 823 1315

Email: msxia6@nottingham.ac.uk

IRAS 193750
REC 16/LO/1693
Patient Information Summary Version 1.1 11/06/18

Key Information

AIMS

To better understand asthma control using technology.

PROCESS

We aim to recruit 50 participants who will use this technology for 6 months.

It will involve a visit to either City Hospital NRRU or your local GP practice at the start and one 6 months later at the end. In between, the study team will keep in touch with you by phone.

WHY ME?

You have been chosen because:

- You have been diagnosed with asthma
- Have been prescribed a pre-venter inhaler
- You have needed tablet steroids in the last year
- You have a mobile phone that can connect to the internet

IRAS 193750
REC 16/LO/1693
Patient Information Summary Version 1.1 11/06/18

WHAT WILL HAPPEN TO ME IF I TAKE PART?

- We will ask you information about your asthma
- You will fill out questionnaires about your asthma symptoms
- We will do a spirometry test to measure the amount of air you can breathe out
- We will provide you with new inhaler casings that clip around your current inhalers. These help tell us how well controlled your asthma is
- We will provide you with a written asthma action plan and check your inhaler technique

We ask you to then carry on as normal. This study should not affect your lifestyle and you should continue to take your normal medication as per usual.

IRAS 193750
REC 16/LO/1693
Patient Information Summary Version 1.1 11/06/18

Participant Consent Form (Main)

Version: 2.3 Date: 11th June 2018

Improving asthma treatment using inhaler technology
Principal Investigator: Dr Dominick Shaw

Patient Study ID: …..…….. Initials: ……

Patient initial each box

1. I confirm that I have read and understand the information sheet version 2.3 dated 11th June 2018 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
3. I understand that my medical records may be looked at by authorised individuals from the Sponsor for the study and the UK Regulatory Authority in order to check that the study is being carried out correctly. ☐
4. I understand that even if I withdraw from the above study, the data collected from me will be used in analysing the results of the trial, unless I specifically withdraw consent for this. ☐
5. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐
6. I agree that my GP, or any other doctor treating me, will be notified of my participation in this study and will be contacted if there are any concerns about my health. ☐
7. I agree to allow researchers to view my medical records (for example, GP or hospital records) to collect information that is related to my asthma or this study. ☐
8. I consent to medication use data being stored on a password-protected website, which may be hosted outside England. ☐
9. I agree to take part in the study. ☐

Name of the patient *(Print)* date

Patient's signature

Name of the person taking consent *(Print)* date

Signature

Original to be retained and filed in the site file, 1 copy to patient, 1 copy to be filed in patient's notes

Participant Consent Form (B)

Version: 2.3 Date: 11th June 2018

Improving asthma treatment using inhaler technology
Principal Investigator: Dr Dominick Shaw

Patient Study ID: …..…….. Initials: ……

Patient initial each box

1. I confirm that I have read and understand the information sheet version (B) 2.3 dated 11th June 2018 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐

3. I understand that my medical records may be looked at by authorised individuals from the Sponsor for the study and the UK Regulatory Authority in order to check that the study is being carried out correctly. ☐

4. I understand that even if I withdraw from the above study, the data collected from me will be used in analysing the results of the trial, unless I specifically withdraw consent for this. ☐

5. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐

6. I agree that my GP, or any other doctor treating me, will be notified of my participation in this study and will be contacted if there are any concerns about my health. ☐

7. I agree to allow researchers to view my medical records (for example, GP or hospital records) to collect information that is related to my asthma or this study. ☐

8. I consent to medication use data from my inhaler being stored on a password-protected website, which may be hosted outside England. ☐

9. I agree to my inhaler medication use being sent to researchers. I understand that I may be contacted to discuss my asthma. ☐

11. I agree to take part in the study ☐

Name of the patient *(Print)*	date
Patient's signature	
Name of the person taking consent *(Print)*	date
Signature	

Original to be retained and filed in the site file, 1 copy to patient, 1 copy to be filed in patient's notes

Participant Consent Form (Qualitative Interview)

Version: 1.2 Date: 11th June 2018

Improving asthma treatment using inhaler technology
Principal Investigator: Dr Dominick Shaw

Research Fellow: Dr Ireti Adejumo

Patient Study ID: …..…….. Initials: ……

Patient initial each box

1. I confirm that I have read and understand the information sheet version 2.3 dated 11th June 2018 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
3. I consent to participate in the 'qualitative interview' part of this study. ☐
4. I understand that this will involve an audio recording of the interview and that this recording will be kept for use in the study. ☐
5. I understand that the audio recording of the interview will not use any personal identifiers to identify me. ☐
6. I understand that the audio recording of the interview may be released to a trusted transcription service. ☐

_____ _____
Name of the patient *(Print)* date

_____
Patient's signature

_____ _____
Name of the person taking consent *(Print)* date

_____
Signature

Original to be retained and filed in the site file, 1 copy to patient, 1 copy to be filed in patient's notes

Appendix E: Semi-structured interview guide

The interview guide

Semi-Structured Interview Guide

1. Introduction

Explain the purpose of the interview in general:

'We would like to hear how you felt about:
- Your participation in the Smartinhaler™ study
- Your views on the device
- Your views on the collection of personal electronic data from your Smartinhaler™
- Your views on the collection of personal electronic data from your mobile phone.'

Check consent form has been signed and check still happy to take part.

1. Give statement on confidentiality, right to withdraw consent, recording of the interview:

'We would like to reassure you that all data relating to yourself will be kept strictly confidential by the research team. The recording of this interview and any quotes used in study reports will not identify you in any way. Your participation is entirely voluntary and you are free to stop the interview at any time without giving a reason.We will retain any information collected to this point unless you specify otherwise.'

2. Ask if the participant has any questions before starting the interview.
3. Explain that the interview will last between 30 and 45 minutes.

2. Background

Discussion of baseline asthma control

1. Tell me about your asthma – how is it normally? – how does it affect you?
2. How long have you had asthma for? How has it been treated over the years?
3. To what extent do you feel you're in control of your asthma?
a. How often you're getting symptoms
b. The effect it's having on your life
c. The number of times you're needing to see your GP/go to hospital
4. What did you think of your inhalers prior to enrolling in the study?
a. Did you feel you needed them?
b. How effective were they for your asthma?
c. According to your prescription, how regularly was your preventer inhaler meant to be used?
d. How regularly did you use your preventer? Explore.
e. Did you use any prompts to remember to use your preventer (e.g. phone alarms, calendar reminders)?
f. How did you feel about using them publicly?

Exploration of baseline health beliefs

1. How important do you feel it is to take your preventer inhaler regularly?
a. If I made the statement "Regular use of your inhalers as prescribed is **crucial** to preventing your asthma from getting worse or flaring up," would you find yourself able to agree or would you have to disagree?
b. What makes you feel this way?
2. How important do you feel it is to take your other asthma medication regularly?
a. What makes you feel this way?

3. Smartinhaler™ Experience

Discussion opening

1. Can you share your general thoughts on the device you have been using?
a. What did you think of it?
b. How did it compare to using your inhaler without the device?
c. How easy was it to carry around? Is this any different to your normal inhaler?
d. How easy was it to use in public? Is this any different to your normal inhaler?

3. Smartinhaler™ Experience

Exploration of perceived impact on inhaler usage subsequent to being informed of monitoring

1. To what extent do you think your participation in the study impacted the use of your inhaler?
a. Did it impact how regularly you used your preventer?
b. Did it impact how regularly you used your reliever?
c. Do you feel it changed how you used your inhalers in any other way?
d. Do you feel it changed how important you feel taking your preventer regularly is?
2. I asked earlier whether you used any prompts before to remind you to use your inhalers.
a. Did you find you used any prompts during the study?
b. Did you find yourself more or less in need of those prompts during the study?

Discussion of response to feedback

1. Can you tell me about any feedback you received?
a. Through the smartphone app?
b. From your GP/practice nurse?
c. From your hospital clinician?
d. From any other sources?
2. How did the feedback make you feel?
3. How useful was the feedback?
4. How clear was the feedback?
5. Can you suggest any ways in which the provision of the feedback could be improved?

Discussion of effect of participation on other aspects of self-management.

1. To what extent has participation in the study helped with how well your asthma has been controlled?
a. How often you're getting symptoms
b. The effect it's having on your life
c. The number of times you're needing to see your GP/go to hospital
2. To what extent has participation in the study helped with how well *you* have been able to take control of your asthma?
3. Have you learnt more about your asthma from participating in this study?

3. Smartinhaler™ Experience

Exploration of reaction to monitoring

1. What were you told about the device when it was given to you?
2. Were you aware that the way you used the inhaler was being monitored?
a. **If yes**: what do you think was being monitored?
i. What did you think about this? How did it make you feel?
ii. If you hadn't been aware you were being monitored, would that change how you feel now?
iii. To what extent did knowing you were being monitored change the way used your inhaler?
b. **If no:** what do you think might have been monitored?
i. Explain monitoring took place
ii. Explain what was monitored
iii. 'How do you feel about this?'
iv. If you had been aware …… was being monitored, would that change how you feel now?

4. Data Capture

1. If, in the future, we started monitoring inhalers like we did with you, who, in your opinion, should be responsible for keeping an eye on the data?
a. E.g. You? Your GP/practice nurse? The hospital?
b. What makes you feel this way?
2. Where do you feel that healthcare-related data like this should be stored? **(NB these are NOT your medical records)**
a. E.g. on the company's database? On a GP or hospital database?
3. If, in the future, we started monitoring inhalers like we did with you, who, in your opinion, should be responsible for providing the feedback?
a. E.g. Your GP/practice nurse? The hospital? A dedicated lay service?
b. How should it be provided? (text, email, web link, phone call etc)
4. Who do you feel has the ultimate responsibility for your asthma at the moment?
a. Who should have/would you like to have responsibility for it?
b. Who else might help you in controlling your asthma symptoms?

4. Data Capture

5. How would you feel about data on how you use your inhaler being linked to data on your asthma triggers (local pollen levels, for example)?
a. How would you feel about the use of location tracking via GPS to increase the accuracy of this?
b. Do you feel there is a possibility this could be used to help with your asthma?
6. How would you feel about linking information from fitness or healthcare apps you already use or might use in the future to give us more information relevant to your asthma?
7. Is there anything else you feel we could collect data on that might help us get a better idea of the factors involved in what makes your asthma easy/hard to control?
8. Is there any type of data capture (information on your asthma that we could collect using technology) that makes you nervous?
9. Who do you think should or shouldn't have access to this sort of data?

5. Future applications

1. Would you consider using a Smartinhaler™ regularly?
a. What are the main reasons you think/don't think so?
2. How would you feel if your GP or consultant provided you with a Smartinhaler™ permanently/for a short period of time?
3. How do you think your GP or consultant might use the data obtained from it?
4. How would you feel if your GP or consultant/another healthcare professional/a nonhealthcare professional:
a. Discussed the data they had obtained from it with you?
b. Asked you to change something based on this data?
c. Carried out an emergency intervention based on this data?
d. Used it to monitor your response to treatment?
5. How often do you think these discussions should take place? *E.g. monthly, as and when needed*
6. How would you feel if this information was shared with other members of your healthcare team?
7. How would you feel about this data being used to inform what treatment you are/are not prescribed?
a. For example, we may consider using them to tell us if people can start newer medications for asthma in the future. How would you feel about them being used in this way?
b. If Smartinhalers™ were to be used in this way, do you think they would impact the way your GPs interact with you? *E.g. your annual asthma review*
i. If so, how? If not, why?
ii. How do you feel about this?

6. Smartinhaler™ going forward

1. Can you think of any ways in which the Smartinhaler™ could be designed differently?
a. Is there anything in the design of the device that:
i. Could be improved?
ii. Would make it easier to use?
iii. Would make you more likely to want to use it?
b. Is there anything in the design of the app that:
i. Could be improved?
ii. Would make it easier to use?
iii. Would make you more likely to want to use it?
2. How would you feel if there was no casing at all and the Smartinhaler™ was just part of your inhaler?
3. Would you ever consider purchasing a Smartinhaler™ for use yourself? Why/why not?
4. How much do you think the Smartinhaler™ costs?
a. What do you think about the cost?
b. How does this affect whether you would consider purchasing one?
5. Can you think of anything else the Smartinhaler™ might add
a. To your current care?
b. To the way we manage asthma in general?

7. Closing Remarks

1. Is there anything that we haven't talked about that is important to you and that
you'd like to add?
2. Do you have any questions for me?
3. Thank the participant for their time.