Study Protocol: CRITIKAL Study

ASSESSING THE ASSOCIATION BETWEEN PATIENT FACTORS AND INHALER TECHNIQUE WITH ASTHMA CONTROL IN PATIENTS RECEIVING FIXED DOSE COMBINATION THERAPY (FDC) INHALED CORTICOSTEROID / LONG-ACTING BETA AGONIST (ICS/LABA) ± SHORT-ACTING BETA$_2$-AGONIST (SABA) THERAPY

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1 Introduction

1.1 Background

Asthma is a chronic inflammatory condition of the airways. Poorly controlled asthma has a substantial impact on quality of life and healthcare resources.[1,2] Much work remains to optimise asthma management.[3]

Factors that influence treatment benefits include diagnostic inaccuracy, smoking, comorbid rhinitis, non-adherence and other pyscho-social factors.[3–8] In addition, exploratory work using the UK Clinical Practice Research Database (CPRD) suggests that inhaler device type, and effective inhalation technique, may play an important role in achieved asthma control outcomes.[9]

Similarly, the International Primary Care Respiratory Group (IPCRG) identified poor inhaler technique as an important reason for continuing sub-optimal asthma control.[3] To date, only a small number of studies have addressed inhaler technique and these looked at patients receiving inhaled corticosteroid therapy only.[10] The IPCRG called for more research to identify how individual factors may predict patient response to treatment, particularly in primary care where most asthma is managed, and to use pragmatic and observational studies to reflect more closely the realities of managing a patient population with widely heterogeneous characteristics.[3]

The Helping Asthma in Real-life Patients (HARP) initiative was established in 2010 to validate clinical assessment tools in clinical practice[11]. The initiative comprises a questionnaire that enables consistent data collection about a patient's asthma, including asthma control and treatment adherence, and offers feedback based on guideline recommendations to the health practitioner managing a patient.

The iHARP review service seeks to implement the goals of the HARP initiative. The iHARP review uses the HARP questionnaire and an assessment of inhaler technique carried out by trained nurses/pharmacist to appraise patients and offer training on inhaler technique and feedback.

Over 5000 iHARP patient reviews were carried out between 2011 and 2014 across Europe and Australia. Anonymised data from these reviews provide a valuable data source that will be utilised in this study, to evaluate characteristics associated with serious and potentially serious inhaler errors performed by patients in routine care. Serious inhaler errors are defined as errors that are likely to results in no drugs dose being received by the patient, and potentially serious errors those that are likely to reduce the drug dose.

In this study the role of inhaler technique and other factors will be assessed to determine their prognostic ability to predict the level of asthma control achieved by patients. A summary of 'critical errors' (errors that adversely affect asthma control) in inhaler techniques will also be produced to potentially enable more reliable targeting of faults for patients training programmes.

1.2 Study aims and research questions

1.2.1 Aims

To assess the association of patient/treatment factors, including inhaler technique, treatment adherence and comorbidities, with asthma control in patients receiving fixed dose combination therapy (FDC), inhaled corticosteroids/long-acting beta agonists (ICS/LABA), ± short-acting beta2-agonist (SABA) therapy.

A further aim will be to identify errors in inhalation technique that constitute 'critical errors' defined as those that have an adverse effect on asthma control.

1.2.2 Objectives

The primary objective of this cross sectional study is to establish the prognostic role of patient/treatment factors in predicting asthma control in patients with stable asthma receiving combination therapy.

The secondary objective will be to identify 'critical errors' in inhalation technique that affect asthma control.

1.3 Data Sources

Data have been sourced from the initiative iHARP dataset and OPCRD.

1.3.1 iHARP dataset

The iHARP dataset is a unique international dataset made up of anonymised patient data from patients invited to complete an iHARP asthma review. Patients have been recruited from the UK, the Netherlands, Norway, Spain, Italy, Sweden, Australia and France. Data are collected at the point of recruitment via the iHARP review. Recruitment was initiated in June 2011 and is ongoing. Results used in this study were last updated in December 2014.

Patients were selectively invited for an iHARP review. The invited patients met certain criteria including having a current asthma diagnosis and not having diagnosed COPD. The invited patients were not known to be prescribed ICS separately in addition to FDC ICS/LABA therapy, and were not receiving systemic treatments for asthma such as maintenance oral steroids, theophylline, leukotrience receptor antagonists or anti-IGE therapy.

Data are collected via clinician reviews and included patient reported data such as symptoms, smoking status, comorbidity, treatment, adherence, subjective and objective inhaler technique, lung function, and nitric oxide (NiOX) readings.

For patients within the UK, the above data are combined with routinely collected clinical data from the Optimum Patient Care Research Database (OPCRD).

1.3.2 OPCRD

Optimum Patient Care (OPC) extracts anonymous data from practices to perform reviews of their chronic respiratory services. Two types of anonymised patient data are typically collected:

Routine clinical data

- OPC software interfaces with primary care practice management systems and extracts disease coding and prescribing information

Questionnaires

- Patients identified as recipients of the respiratory service under review are invited to complete validated disease assessment questionnaires to better understand their current health status (and/or possible reasons for sub-optimal status)
- Anonymised questionnaires are assigned a unique code to aid matching routine data to questionnaire results

The OPCRD, which comprises the routine clinical and questionnaire data, has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The database is increasing in size daily, but at last validated review included data from nearly 2 million patients captured across almost 600 medical centres across the UK.

The anonymised, longitudinal patient data offer a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad-range of respiratory areas and, in contrast to other medical research databases (e.g. the Clinical Practice Research Database [CPRD]) OPCRD data, offers the additional dimension of patient reported outcomes.

1.4 Study design

This is a historical, real-world, cross-sectional observational study using data from the iHARP dataset and the OPCRD.

The population of patients in the iHARP database will be classified by their disease severity based on Global Initiative for Asthma (GINA) classification (controlled, partly controlled and uncontrolled) and/or the Asthma Therapy Assessment Questionnaire (ATAQ). The proportion and odds of a patient performing a range of device errors will be interpreted and classified).

1.4.1 Study period

The study will be conducted using data collected by the iHARP review service between June 2011 and February 2015.

1.4.2 Recorded errors

Inhaler device and drugs:

This comprises a subjective technique assessment as recorded by the health care practitioner and an objective technique assessment as assessed by available Spirotrac data and Aerosol Inhalation Monitor (AIMS) data.[12] The subjective assessment involves a number of errors evaluated as 'serious' and 'potentially serious'* for each of the following types of inhaler device:

- Fluticasone / salmeterol (FP/SAL; Seretide®) via Diskus Dry Powder Inhaler (DPI)
- FP/SAL (Seretide®) via Metered Dose Inhaler (MDI)
- Budesonide / formoterol (BUD/FOR; Symbicort®) via Turbuhaler (including patients on SMART-use as maintenance and reliever-therapy)
- Beclometasone dipropionate/ formoterol (BDP/FOR; Fostair®) via MDI

1.4.3 Other recorded factors

Peak inhalation flow:

The objective assessment involves Peak Inhalation Flow (PIF) measures and AIMS data according to which each patient's acceleration reading will be classified as:

- Acceptable
- Potentially critical
- Critical

Adherence:

MARS adherence was reported using the Medication Adherence Rating Scale (MARS) score. This measures adherence on a 6-point scale (never, rarely, sometimes, regular, often and always) in response to the following questions about their preventer inhaler use:

- I use it only when I feel breathless
- I avoid using it if I can
- I forget to take it
- I decide to miss a dose
- I choose to take it once a day

Adherence was categorised as: poor (any of the questions answered with 'often' or 'always'), borderline (more than one questions with 'sometimes') and good (none of above).

* Classification was made following advice from clinical experts, where 'Serious' is no drug dose is likely to be received by the patient and 'Potentially serious' a reduced drug dose is likely to be received the patient

1.5 Study population

Patients were selectively invited for an iHARP review. The invited patients met certain criteria including having a current asthma diagnosis and not having diagnosed COPD.

1.5.1 Inclusion criteria

Patients must meet the following inclusion criteria:

- Aged 16+ years at the date of their iHARP review
- Receiving current asthma therapy as FDC ICS/LABA:
    - ≥1 prescriptions for FDC ICS/LABA in the year prior to review via:
        - DPI or
        - MDI with or without a spacer device
- Completed asthma review during which full study-relevant data were recorded, meeting standards of IPCRG, Global Initiative for Asthma (GINA) guidelines and Quality and Outcomes Framework (QOF) recommendations[13]

1.5.2 Exclusion criteria

Patients will be excluded from the analysis if they:

- Have received oral corticosteroids and/or antibiotics for a lower respiratory condition (identified using lower respiratory diagnoses) in the 2 weeks preceding their asthma review (used as a proxy measure for identifying an asthma exacerbation and / or lower respiratory infection, which might suggest unstable disease)
- Are receiving long-term, systemic treatments for asthma including maintenance oral steroids, theophylline, leukotriene receptor antagonists (LTRA) or anti-IgE therapy (i.e. omalizumab)

Sensitivity analyse will also be carried out on the sub population of patients receiving LTRAs.or theophylline.

1.6 Sample size and power calculation

The power calculations for the study were based on the following data:

- Overall, 60% of subjects are estimated to have good inhaler technique (40% will not)[10]
- Among those with good inhaler techniques, 70% have good asthma control[14]

The total sample size needed is 4482 (1793 and 2689 for those making no errors and those making errors respectively).

A 5% decrease in asthma control (from 0.7 to 0.65, i.e. OR=0.8) is obtained between Group 1 proportion (0.70 is the proportion of patients with no critical errors who are controlled) and Group 2 (0.65 is the proportion of patients making at least one critical error who are controlled). Using a binary covariate in an unbalanced design (40% making no errors and 60% making errors) and a squared multiple correlation coefficient R=0.1 for the additional covariates at 5% level of significance with 90% power.

1.7 Study outcomes

1.7.1 Primary outcomes

Asthma Control:

Where asthma control is assessed by an GINA evaluation/classification[15] incorporated into the iHARP questionnaire (questions about symptoms in the last 7 days) (Appendix 1) defined as:

Reported symptoms from previous week	**GINA control level**		
	Controlled	Partly controlled	Uncontrolled
Daytime symptoms (more than twice/week)	None of these	1 or 2 of these	3 or 4 of these
Any night waking due to asthma			
Needed reliever inhaler (more than twice/week)			
Any limitation to day time activity			

1.7.2 Secondary outcomes

Risk assessment

Number of asthma exacerbations in the year preceding iHARP review will be defined from the number of courses of oral corticosteroids reported by the patients as prescribed in response to worsening asthma. Patient-reported oral corticosteroid courses on iHARP review questionnaires (Appendix 1), when the health care professionals asked the following question: "How many courses of oral corticosteroids have you received in the last 12 months for worsening asthma?".

Patients will be classified as:

- **Higher risk:** if they have had ≥2 exacerbations in the previous year
- **Moderate risk:** if they have had 1 exacerbation in the previous year
- **Lower risk:** if they have had 0 exacerbations in the previous year

1.8 Covariates

Prior research in respiratory disease has identified a range of potential confounders that may impact on study outcomes. These include education, smoking, medication, comorbid allergic rhinitis and other co-morbid diseases and medications. These variables will be extracted, where available, for all patients (example results tables are presented in Appendix 3).

Potential confounders obtained during the iHARP review:

- Age of patient at time of review / assessment
- Gender
- Body mass index (BMI) (i.e. height and weight measurements) at time of assessment / asthma review
- Smoking status at time of iHARP assessment and packs per year for current smokers and ex-smokers
- Socio-economic status marker (Highest Education attainment)
- Duration of asthma
- Unrelated co-morbidities expressed using the Charlson Comorbidity Index (CCI)
- Presence / absence of comorbid allergic rhinitis (diagnosis ever and / or ≥2 prescriptions for rhinitis therapy in the prior year
- Presence of patient reported rhinitis and severity
- Where comorbid allergic rhinitis is present, use of nasal corticosteroids for its treatment
- Presence / absence of comorbid eczema (diagnosis ever and / or ≥2 prescriptions for eczema therapy in the prior year)
- Presence of Gastroesophageal Reflux Disease (GERD)(diagnosis ever and / or ≥2 prescriptions for GERD therapy in the prior year)
- Presence of cardiac disease (diagnosis ever and / or ≥2 prescriptions for cardiac drugs in the prior year
- Side effects including: continual sore mouth/throat, oral thrush, bruising, hoarse voice, abnormal weight gain and cough
- Presence of co-morbid diseases including connective tissue disease, chronic pulmonary disease, congestive heart failure, myocardial infarction, tumours, peripheral vascular disease, ulcer diagnosis, leukaemia, dementia, liver disease, lymphoma, diabetes mellitus, hemiplegia, cerebrovascular disease, moderate or severe renal disease, AIDs.
- Number of paracetamol prescriptions in prior year where known otherwise approximate frequency of use (as regular, intermittent or not used)
- Number of asthma exacerbations in the year preceding iHARP review, defined as a course oral corticosteroids reported as being in response to worsening asthma
- Number of hospital outpatient attendances in the prior year where asthma and / or other lower respiratory illness was the reason for referral
- Current prescribed combination therapy

Further potential confounders obtained for UK patients to be extracted from the OPCRD database including:

- Current recommended ICS dose prescribed at assessment date
- Number of prescriptions for any respiratory therapy in the prior year
- Average ICS daily dose during the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days)
- Change in therapy in the prior year, where change is defined as: increase in dose (≥50% increase in ICS dose), additional therapy or switch to a different therapy in the same class
- Number of short-acting beta-agonist (SABA) prescriptions received in the prior year
- Average daily SABA dose
- Number of prescriptions for any antibiotic in the prior year where the reason for the prescription is lower-respiratory tract infection
- Number of beta-blocker prescriptions in the prior year (split by oral and topical therapy)
- Number of non-steroidal anti-inflammatory drug (NSAID) prescriptions in the prior year where known otherwise approximate frequency of use (as regular, intermittent or not used)
- Number of general practice consultations for asthma that did not result in asthma exacerbations treatment and / or other respiratory illness antibiotics in prior year
- Number of hospitalisations for asthma and / or lower respiratory illness in the prior year (including non-specific hospitalisations with an asthma / respiratory code within a one week window)

1.9 Definitions

1.9.1 Body Mass Index (BMI)

The BMI is a representative measure of body weight based on the weight and height of the subject. It is defined as the weight (in kg) divided by the square of the height (in m) and is measured in kg/m^2. BMI will be categorised as follows: underweight (< 18.5), normal BMI (18.5 - 24.99), overweight (25-29.99), obese (≥30).

1.9.2 Charlson Comorbidity Index (CCI)

The CCI was developed in the US in 1987 as a method of classifying prognostic comorbidity in longitudinal studies[16]. It predicts the one-year mortality for a patient who may have a range of comorbid conditions such as heart disease, AIDS or cancer. Each condition is assigned a "weight" depending on the risk of dying associated with the condition; scores are then summed to give a total score predicting mortality.

The weights were revised and updated (for example, mortality due to HIV has fallen) by Dr Foster Intelligence (DFI) in their HSMR Methodology documentation[17] and calibrated using UK data (due to differences in coding practice and hospital patient population characteristics from the US), using ICD-10 codes. As a result:

- DFI have expanded the coding definition of some conditions;
- Only secondary diagnoses (DIAG02-DIAG14) are now considered;
- There is greater variation in weights between conditions and the Charlson Index (the sum of the weights) can be treated as a continuous variable (limited to the range 0-50) for the purposes of risk adjustment.

The weights, codes and conditions used in this study are summarised in Table 1.

Table 1 Co-morbid conditions and scores used in the Charlson Co-morbidity Index (CCI)

Condition	Condition name	ICD-10 codes	Weight
1	Acute myocardial infarction	I21, I22, I23, I252, I258	5
2	Cerebral vascular accident	G450, G451, G452, G454, G458, G459, G46, I60-I69	11
3	Congestive heart failure	I50	13
4	Connective tissue disorder	M05, M060, M063, M069, M32, M332, M34, M353	4
5	Dementia	F00, F01, F02, F03, F051	14
6	Diabetes	E101, E105, E106, E108, E109, E111, E115, E116, E118, E119, E131, E131, E136, E138, E139, E141, E145, E146, E148, E149	3
7	Liver disease	K702, K703, K717, K73, K74	8
8	Peptic ulcer	K25, K26, K27, K28	9
9	Peripheral vascular disease	I71, I739, I790, R02, Z958, Z959	6
10	Pulmonary disease	J40-J47, J60-J67	4
11	Cancer	C00-C76, C80-C97	8
12	Diabetes complications	E102, E103, E104, E107, E112, E113, E114, E117, E132, E133, E134, E137, E142, E143, E144, E147	-1
13	Paraplegia	G041, G81, G820, G821, G822	1
14	Renal disease	I12, I13, N01, N03, N052-N056, N072-N074, N18, N19, N25	10
15	Metastatic cancer	C77, C78, C79	14
16	Severe liver disease	K721, K729, K766, K767	18
17	HIV	B20, B21, B22, B23, B24	2

1.9.3 Device errors

Device errors have been grouped into generic (common to all devices) and device-specific categories (variable codes in Appendix 2) and by phase of procedure (preparation, inhalation and general knowledge), classified following discussion with clinical advisors.

The types of error have been classified as:

- **Serious** – no drugs dose is likely to be received by the patient
- **Potentially serious** – a reduced drug is likely to be received the patient

The stages of inhaler use have been classified as:

- **Preparation** – actions that require the inhaler device, but do not involve inhaling, including removing cover and dose preparation
- **Inhalation** – actions that require the inhaler device and that involve inhaling, including emptying lungs, device actuation, inhaling and breath hold
- **General Knowledge** – actions that do not require the inhaler device or involve inhaling, including knowledge off how to know when the device is empty or expired and spacer care

Table 2: Generic errors (all devices)

Manoeuvre	**Classification**
Preparation	
Does not remove cap/slide cover fully open	Serious error
Inhalation	
Does not breathe out to empty lungs	Serious error
Does not have head tilted such that chin is slightly upwards	Potentially serious error
Does not inhale	Serious error
Inhales through the nose	Serious error
No breath-hold (or holds breath for less than 3 seconds)	Potentially serious error
Second does within 30 seconds	Potentially serious error
Does not repeat the second inhalation, if needed	Potentially serious error
After last inhalation does not replace cap/cover	Potentially serious error
General Knowledge	
Patients' has expired inhaler	Potentially serious error
Patients' cannot tell whether their inhaler is empty	Serious error
Patients' did not bring their own inhaler to the clinic	Potentially serious error

Table 3: DPI Diskus – specific

Manoeuvre	Classification
Preparation	
Shakes Diskus inhaler after dose preparation	Serious error
Holds inhaler in a downward position after dose preparation (before inhalation)	Serious error
Exhales into the inhaler before inhalation	Serious error
Inhalation	
Inhalation is not fast, forceful from the start and as long as possible	Potentially serious error
Does not put inhaler in mouth and seal lips around mouthpiece	Serious error
General Knowledge	
None	

Table 4: DPI Turbuhaler specific errors

Manoeuvre	Classification
Preparation	
Shakes Turbuhaler during preparation	Serious error
Dose not twist the base of the Turbuhaler until it clicks and/or turn back to original position	Serious error
Shakes inhaler after dose preparation	Serious error
Dose not hold the inhaler upright (mouthpiece skywards +/- 45°) when twisting the base during dose preparation	Serious error
Exhales into inhaler before inhalation	Serious error
Inhalation	
Inhalation not fast, forceful from the start and as long as possible	Potentially serious error
Does not put inhaler in mouth and seal lips around mouthpiece	Serious error
General Knowledge	
None	

Table 5: MDI specific errors

Manoeuvre	Classification
Preparation	
Does not shake before actuation	Serious error
Exhales into inhaler	Potentially serious error
Does not hold inhaler upright	Serious error
Inhalation	
Does not coordinate actuation with inhalation; actuation before inhalation	Serious error
Does not coordinate actuation with inhalation; actuation is too late	Potentially Serious error
Does not inhale slowly and deeply - defined as at least 3 seconds	Potentially serious error
Does not actuate	Serious error
Coughs during inhalation	Serious error
General Knowledge	
If on Fostair – knowing that inhaler can only be used for up to 20 weeks/5 months	Serious error
Does not mention priming when asked: What do you do when you haven't used your inhaler for: Evohaler, 1 week; or Fostair, 2 weeks?	Potentially serious error
Does not mention priming when asked: What do you do when you use your inhaler for the first time?	Potentially serious error

Table 6: MDI with spacer specific errors

Manoeuvre	Classification
Preparation	
Does not know how to correctly assemble the spacer	Serious error
Does not shake before placing into spacer	Serious error
Does not insert mouthpiece into spacer and ensure a tight seal	Serious error
Does not hold spacer with inhaler upright	Serious error
Inhalation	
Put spacer mouthpiece in mouth but does not seal lips	Potentially serious error
Does not actuate a dose into the spacer (none or more than 1)	Serious error
Does not start to inhale through mouthpiece within 2 seconds of actuating one dose	Serious error
Does not inhale slowly, steady and deeply - defined as at least 3 seconds (may use tidal breathing this should be slow and relaxed [not panting])	Serious error
Aerochamber whistles during inhalation	Potentially serious error
Coughs during the inhalation	Serious error
General Knowledge	
If on Fostair – knowing that inhaler can only be used for up to 20 weeks/5 months	Serious error
Does not mention priming when asked: What do you do when you haven't used your inhaler for: Evohaler, 1 week; or Fostair, 2 weeks?	Potentially serious error
Does not mention priming when asked: What do you do when you use your inhaler for the first time?	Potentially serious error
Spacer has any faulty parts, valves, or cracks in the plastic	Serious error
Does not wash in soapy /detergent water at least once a week	Serious error
Rinses only with water instead of washing with soap	Serious error
Does not air dry	Serious error
Dries with a cloth	Serious error

1.9.4 PIF and AIMS

PIF and AIMS data were captured for entry into the iHARP database using the form shown in Table 7.

Table 7: Form for data capture

Data capture											
IV (L)											
PIF (L/min)											
Time of inhalation (from 0 sec)*											
Average acceleration rate over time to PIF (L/s^2)											
90% PIF (L/min)											
Time to 90% PIF (from 0 sec)*											
Average acceleration rate over time to 90% PIF (L/s^2)											
PIF over time (L/min)		Time (seconds)									
		0.1	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.5	End inspiration
PIF (L/s) when IV is	200ml										
	300ml										
	500ml										
Acceleration rate (L/min^2)		Time (seconds)									
		0.1	0.2	0.3	0.4	0.5	0.6	0.8	1.0	1.5	End inspiration
Acceleration (L/s^2) when IV is inhaled volumes	200ml										
	300ml										
	500ml										

PIF: peak inhalation flow; **IV**: inhalation volume; **L**: litres; **min**: minutes; **secs**: seconds

*May be set to 3L/min to reduce noise

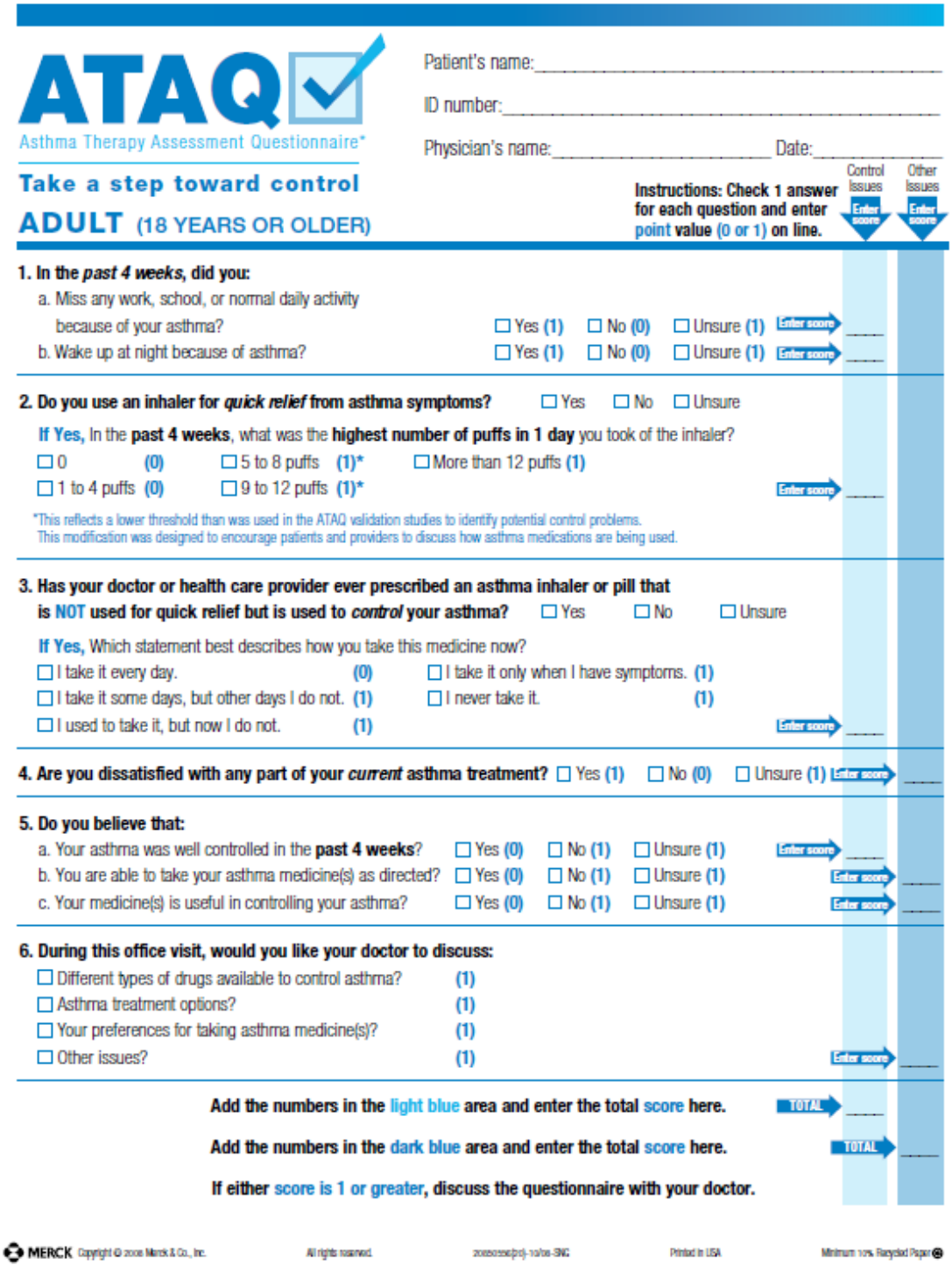
Patient's acceleration will be classified as:

	MDI PIF L/min	Diskus for L/min at 0.4 sec	Turbuhaler for L/min at 0.4 sec
acceptable	30 to 90	>30	>60
potentially serious	90-150		30-60
Serious	>150	<30	<30

The acceleration required with DPIs the criteria is the flow at 0.4 seconds[18]. Acceleration is not an issue with MDIs[19,20].

1.9.5 Asthma therapy assessment questionnaire (ATAQ)

ATAQ data were captured for entry into the iHARP database using the standard ATAQ form shown in Figure 1.



ATAQ

Asthma Therapy Assessment Questionnaire*

Take a step toward control

ADULT (18 YEARS OR OLDER)

Patient's name: _____

ID number: _____

Physician's name: _____ Date: _____

Instructions: Check 1 answer for each question and enter point value (0 or 1) on line.

Control Issues Enter score | Other Issues Enter score

1. In the *past 4 weeks*, did you:
   a. Miss any work, school, or normal daily activity because of your asthma? ☐ Yes (1) ☐ No (0) ☐ Unsure (1) Enter score ____
   b. Wake up at night because of asthma? ☐ Yes (1) ☐ No (0) ☐ Unsure (1) Enter score ____

2. Do you use an inhaler for *quick relief* from asthma symptoms? ☐ Yes ☐ No ☐ Unsure
   If Yes, In the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?
   ☐ 0 (0) ☐ 1 to 4 puffs (0) ☐ 5 to 8 puffs (1)* ☐ 9 to 12 puffs (1)* ☐ More than 12 puffs (1)
   Enter score ____
   *This reflects a lower threshold than was used in the ATAQ validation studies to identify potential control problems. This modification was designed to encourage patients and providers to discuss how asthma medications are being used.

3. Has your doctor or health care provider ever prescribed an asthma inhaler or pill that is NOT used for quick relief but is used to *control* your asthma? ☐ Yes ☐ No ☐ Unsure
   If Yes, Which statement best describes how you take this medicine now?
   ☐ I take it every day. (0) ☐ I take it only when I have symptoms. (1)
   ☐ I take it some days, but other days I do not. (1) ☐ I never take it. (1)
   ☐ I used to take it, but now I do not. (1)
   Enter score ____

4. Are you dissatisfied with any part of your *current* asthma treatment? ☐ Yes (1) ☐ No (0) ☐ Unsure (1) Enter score ____

5. Do you believe that:
   a. Your asthma was well controlled in the past 4 weeks? ☐ Yes (0) ☐ No (1) ☐ Unsure (1) Enter score ____
   b. You are able to take your asthma medicine(s) as directed? ☐ Yes (0) ☐ No (1) ☐ Unsure (1) Enter score ____
   c. Your medicine(s) is useful in controlling your asthma? ☐ Yes (0) ☐ No (1) ☐ Unsure (1) Enter score ____

6. During this office visit, would you like your doctor to discuss:
   ☐ Different types of drugs available to control asthma? (1)
   ☐ Asthma treatment options? (1)
   ☐ Your preferences for taking asthma medicine(s)? (1)
   ☐ Other issues? (1)
   Enter score ____

Add the numbers in the light blue area and enter the total score here. TOTAL ____

Add the numbers in the dark blue area and enter the total score here. TOTAL ____

If either score is 1 or greater, discuss the questionnaire with your doctor.

Figure 1 Standard ATAQ form. The ATAQ variable is categorised by: a. Well (0 points); b. Not well (1-2 points); c. Poorly controlled (≥3 points). Note that question 5 of the ATAQ will score 1 point if the answer is 'no'.

1.9.6 Drug codes

Table 8: Drug list

Drug type		Drug class
GERD drugs		Proton-pump inhibitors
Cardiac drugs		Positive inotropic drugs
		Diuretics
		Anti-arrhythmic drugs
		Hypertension and heart failure
		Nitrates, Calcium-channel blockers and other antianginal drugs
		Beta-adrenoceptor blocking drugs
Beta-blockers		Beta-adrenoceptor blocking drugs
NSAIDS		Non-steroidal anti-inflammatory drugs
Paracetamol		Paracetamol
Respiratory drugs	SABA	Short acting beta-agonists
	SAAC	Short acting antimuscarinics
	LAAC	Long acting antimuscarinics
	LABA	Long acting beta-agonists
	FD combinations	Fixed dose combinations of inhaled corticosteroids and long acting beta-agonists
Antibiotics		Aminoglycosides
		Antileprotic drugs
		Antipseudomonal penicillin
		Antituberculous drugs
		Broad-Spectrum penicillin
		Clindamycin
		Macrolides
		Mecillinams
		Metronidazole and tinidzole METRONIDAZOLE AND TINIDZOLE
		Penicillinase-resistant penicillin
		Quinolones Q
		Some other antibacterials
		Tetracyclines
Allergy drugs	Rhinitis	Nasal cromones
		Nasal steroids
	Rhinitis/eczema	Antihistamines
	Eczema	Topical steroids for the skin

2 The Analysis Plan

2.1 General

2.1.1 Software

All analysis will be carried out using R[21] and SPSS.[22]

The level of statistical significance will be 5% while the Benjamini & Hochberg[23] method will be used to control for false discovery rate, the proportion of false discoveries among the rejected hypotheses when assessing 'critical' errors.

2.2 Analyses

Exploratory data analysis will be carried out for all explanatory and outcome variables. Full details are given in section 4.

Statistical analysis of exposures will be carried out via primary and secondary effectiveness outcomes. Full details are given in section 4.

2.2.1 Spirotrac and AIMS Sub-group analyses

Sub-analyses will be carried out for the following sub groups:

1. **Spirotrac sub-group**

   Data fields provided for attainment of 90% peak:

   - Volume (L)
   - Flow (L/s)
   - Flow / time (L/s2)

2. **AIMS2 sub-group**

   Patients' inhalation will be classified (through automated evaluation by the AIMS 2). Each patient's acceleration will be classified as:

   - Acceptable
   - Unacceptable (i.e. potentially critical)

2.2.2 Reported errors in inhaler use sub-group analysis

Sub-analyses with be carried out for clinically defined severity of reported errors. These have been classified as:

- **Serious** – no drug dose is likely to be received by the patient
- **Potentially serious** – a reduced drug dose is likely to be received the patient

Sub-analyses will be carried out for different aspect of reported inhaler use:

- **Preparation** – actions that require the inhaler but do not involve inhaling, including removing cover and dose preparation
- **Inhalation** – actions that require the inhaler and that involve inhaling, including emptying lungs, devise actuation, inhaling and breath hold
- **General knowledge** – actions that do not require the inhaler or involve inhaling, including knowledge off how to know when the device is empty or expired and spacer care

2.3 Statistical Tests

Table 9: Summary of the statistical tests that may be used in the analysis

Test	Use
Chi-square (χ^2) test	Tests for the association between two categorical variables (data presented in contingency tables).
ANOVA	Nonparametric test to compare the distribution of a variable measured on the interval scale across multiple groups when the variable is not normally distributed.
Univariate logistic regression	Used to examine the impact of individual variables on the odds of levels of an outcome with nominal categories
Multivariable Logistic Regression Model	Used to examine the impact of all predictors simultaneously on the odds of levels of an outcome with nominal categories Comparison will be: • Uncontrolled vs controlled • Uncontrolled and partly controlled vs controlled • Uncontrolled vs controlled and partly controlled
Ordinal Logistic regression model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values. • Uncontrolled vs controlled vs partly controlled
Odds or Risk ratio (OR or RR)	Measure of effect size when the outcome measure is binary (the ratio of 2 odds). Estimated using (multinomial/ordinal) logistic regression.
Likelihood ratio test	It is calculated as -2*log likelihood ratio between a model with a covariate to a model without the covariate. Its value follows a chi-squared distribution and it is used to assess the significance of including a covariate into the model
Akaike's Information Criterion (AIC)	It is used for model comparison. The 'best' model is determined as the one smallest AIC value
Generalised Linear Model with gamma distribution and log link	A generalised linear model used to model data where residuals follow a gamma distribution.

3 Exploratory Data Analysis

3.1 Summary Statistics

Summary statistics will be produced for all explanatory and outcome variables for all the patients and for patients using the different types of inhaler devices (Diskus, Turbuhaler, MDI and MDI with spacers). For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Variance / Standard Deviation
- Range (minimum / maximum)
- Median
- Inter-quartile range (25^{th} and 75^{th} percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Count and percentage by category (distribution)

Example tables are presented in Appendix 4.

3.2 Plots

Plots will be produced for all explanatory and outcome variables. For variables measured on the interval or ratio scale, these will include:

- Frequency plots
- Box and whisker plots

Frequency plots will illustrate the distribution of the variable and whether categorisation may be necessary (for example, if heavily skewed). Box plots will illustrate the location and spread of the variable and identify potential outliers. Plots by treatment group will highlight baseline and outcome differences between treatment groups.

For categorical variables, bar plots will be produced to illustrate distributions and highlight differences between exposure groups.

3.3 Data Preparation

The data will be prepared for analysis by:

- Investigating potential outliers
- Identifying and creating new variables as necessary:
    - Transformations of skewed data (for example, log transformations)
    - Categorisation of heavily skewed data
- Investigating missing data (type of and reason for absence)

3.4 Predictors of outcomes

Bivariate analyses will be carried out to identify those explanatory variables that are predictive ($p < 0.05$) of outcomes. These will be considered as potential confounders when modelling the outcome variables.

4 Effectiveness analysis

4.1 Unadjusted comparisons

4.1.1 Primary Effectiveness outcomes

The numbers and percentages of patients within each type of error category ("the patient has this error", "the patient does not have this error") and/or clusters of errors ("the patients has any error", "the patient does not have any error") will be calculated and cross-tabulated over:

- The GINA based asthma control categories ("controlled", "partly controlled", "uncontrolled")

Chi-squared tests will be used to compare the number of patients between each type of error and asthma control and a p-value reported. In order to control for the false discovery rate due to multiple comparisons an adjusted p-value (using the Benjamini & Hochberg) will be reported as well.

4.1.2 Secondary outcomes

Similar to the analysis of the primary outcomes, numbers and percentages of patients will be cross-tabulated and compared across the categories of:

- Risk assessment ("Higher risk", "Moderate risk", "Lower risk")
- Adherence (both subjective and objective) with three categories ("Poor", "Borderline", "Good")

4.2 Adjusted Comparisons

4.2.1 Primary effectiveness outcome

Asthma control based on the GINA score will be the outcome(s) in an ordinal logistic regression with a number of different type of errors as the exposure variables.

Those errors/clusters of errors that will be identified to be 'serious' in the univariate (unadjusted) analysis, i.e. have a strong adverse association with asthma control ($p < 0.05$), will be used in the multivariable regression, along with potential confounding factors (i.e., those covariates with p-value <0.05), to assess their association simultaneously. This will determine whether the effect of 'serious' errors/clusters of errors on asthma control is modified by the presence of confounding factors.

Variable selection, i.e., the decision to retain or not a confounder factor into the model will be assessed by using the likelihood ratio test, whereas for the comparison of different models, the Akaike's Information Criteria (AIC) will be used and the 'best' model will be the one with the smallest value of AIC.

Finally, the prognostic power of the final model will be assessed by cross-validation. This involves the splitting of the dataset into two datasets: the training and the testing dataset. A machine learning algorithm will be used to build the model on the training dataset and test it on the testing dataset. In this way, the model's predictive values will be assessed on an independent dataset, since the testing dataset, although being part of the original dataset, does not contribute information into the building of the model (i.e., the predicted values of the model do not depend on the observed values of the testing dataset).

4.2.2 Secondary effectiveness outcomes

Similar to the analysis of the primary outcomes numbers and percentages of patients will be cross-tabulated and compared across the categories of:

i. Risk assessment ("At higher risk", "At moderate risk", "At lower risk")
ii. Adherence (both subjective and objective) with three categories ("Poor", "Borderline", "Good")

4.2.3 Presentation of results

All adjusted odds ratios for being uncontrolled vs. controlled, partly controlled vs. controlled, uncontrolled vs. controlled and uncontrolled vs. partly controlled vs. controlled (based on GINA classification) will be presented along with 95% confidence intervals (CIs). Example results tables are presented in Appendix 3.

The same presentations will be used for factors associated with risk, and factors associated with adherence.

5 Regulatory and ethical compliance

This study is designed and shall be implemented and reported in accordance with the criteria of the “European Network Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study” and follows the ENCePP Code of Conduct (EMA 2014).

6 Data dissemination

Once a final version of the protocol will be agreed and reviewed by the advisory group, this study will be registered with www.encepp.eu. Initial results will be presented in poster and/or oral format at appropriate thoracic conferences. At least one manuscript containing more detailed results and methodology will be submitted to a journal specialising in respiratory medicine. Submission for publications will be made as soon as the analyses are completed and the results are verified.

7 Advisory group

The iHARP steering committee:

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9 Timelines

Action	Timeline
Protocol final decision	4 weeks
Preliminary analysis	2 weeks
Statistical analysis	2 weeks
Final report writing	4 weeks
Steering committee feedback	2 weeks
First draft of paper	6 weeks after steering committee feedback

10 References

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: Executive summary of the GINA Dissemination Committee Report. *Allergy Eur. J. Allergy Clin. Immunol.* 2004;59:469-478.

2. Gupta R, Sheikh A, Strachan D, Anderson H. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-526.

3. Haughney J, Price D, Kaplan A, et al. Achieving asthma control in practice: Understanding the reasons for poor control. *Respir. Med.* 2008;102:1681-1693.

4. Price D, Thomas M. Breaking new ground: challenging existing asthma guidelines. *BMC Pulm. Med.* 2006;6(1):S6.

5. 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. *Prim. Care Respir. J.* 2009;18:300-305. doi:10.4104/pcrj.2009.00037.

6. Thomas M, Price DB. Impact of comorbidities on asthma. *Expert Rev. Clin. Immunol.* 2008;4:731-742. Available at: http://informahealthcare.com/doi/abs/10.1586/1744666X.4.6.731.

7. Molimard M, Le Gros V. Impact of Patient-Related Factors on Asthma Control. *J. Asthma* 2008;45(2):109-113.

8. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: An observational study in 3811 patients in primary care. *J. Aerosol Med.* 2003;16:249-254.

9. Price D, Roche N, Christian Virchow J, et al. Device type and real-world effectiveness of asthma combination therapy: An observational study. *Respir. Med.* 2011;105(10):1457-1466.

10. Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur. Respir. J.* 2002;19:246-251.

11. Haughney J, Sims E, Holohan J, Ryan D, Price D. Editorial: Improving clinician-patient communication in asthma: The HARP project. *Allergy* 2010;65:413-414.

12. Vitalograph. Aims. Available at: https://vitalograph.ie/products/inhaler-training/aim. Accessed January 1, 2015.

13. Haughney J, Price D, Barnes NC, Virchow JC, Roche N, Chrystyn H. Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs. *Respir. Med. CME* 2010;3(9):125-131.

14. Duerden M, Price D. Training issues in the use of inhalers. *Dis. Manag. Heal. Outcomes* 2001;9:75-87.

15. GINA. *Pocket Guide for Asthma Management and Prevention*.; 2015. Available at: http://www.ginasthma.org/documents/1

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987;40(5):373-383.

17. Dr Foster intelligence. *Understanding HSMRs*.; 2014.

18. Pauwels R, Newman S, Borgström L. Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. *Eur. Respir. J.* 1997;10(9):2127-2138

19. Everard ML, Devadason SG, Le Souëf PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. *Respir. Med.* 1997;91(10):624-628.

20. Kamin WES, Genz T, Roeder S, et al. Mass Output and Particle Size Distribution of Glucocorticosteroids Emitted from Different Inhalation Devices Depending on Various Inspiratory Parameters. *J. Aerosol Med.* 2002;15(1):65-73.

21. Bacharier LB, Boner a, Carlsen K-H, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;63(1):5-34.

22. IBM. IBM SPSS Statistics. 2013. Available at: www.spss.com/uk/software/statistics/.

23. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. R. Stat. Soc. Ser. B* 1995;57:289 - 300.

Appendix

Appendix 1

UK HARP questionnaire:

Asthma Questionnaire V9.0 10052011

Please take a few minutes to complete the whole questionnaire, following the instructions at the head of each section.

In the last week:	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10+*
How many times have you used your reliever inhaler?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thinking about the last 7 days (please tick one box for each question):	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*
How many days has asthma interfered with your normal activities (eg sport, school, work/housework)?	☐	☐	☐	☐	☐	☐	☐	☐
How many nights have you been affected/woken by asthma symptoms (including cough)?	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you experienced asthma symptoms?	☐	☐	☐	☐	☐	☐	☐	☐

In the past 4 weeks, did you:	*Yes*	*No*	*Unsure*
Miss any work, school, or normal daily activity because of your asthma?	☐	☐	☐
Wake up at night because of asthma?	☐	☐	☐
Believe that your asthma was well controlled?	☐	☐	☐
In general, do you use an inhaler for quick relief from asthma symptoms?	☐	☐	☐

If yes, in the past 4 weeks, what was the highest number of puffs in 1 day you took of the inhaler?	*0*	*1 to 4 puffs*	*5 to 8 puffs*	*9 to 12 puffs*	*More than 12 puffs*
	☐	☐	☐	☐	☐

In the last 12 months:	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10+*
How many times have you needed a course of steroid tablets for worsening asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
How many days have you had off work/education because of asthma?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

How many times have you been admitted to hospital with breathing or chest problems?	☐ *0*	☐ *1*	☐ *2*	☐ *3*	☐ *4*	☐ *5+*
How many times have you been treated in accident and emergency or anywhere other than your GP surgery for your asthma?	☐ *0*	☐ *1*	☐ *2*	☐ *3*	☐ *4*	☐ *5+*

About smoking:

Which best describes you?	☐ *Never smoked*	☐ *Used to smoke, but don't now*	☐ *Still smoking*

	1-5	*6-10*	*11-15*	*16-20*	*21-30*	*31-40*	*41-50*	*50+*
If you smoke or used to smoke, how many do you/did you smoke per day?	☐	☐	☐	☐	☐	☐	☐	☐
If you smoke, or used to smoke, how many years have you smoked/did you smoke?	☐	☐	☐	☐	☐	☐	☐	☐

Smoking can make asthma worse - if you still smoke, would you like support from your GP or practice nurse to quit?	*Yes*	*No*
	☐	☐

About your nose:

Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?	☐ *No*	☐ *Occasionally & little bother*	☐ *Occasionally & quite a bother*	☐ *Most days but little bother*	☐ *Most days & a lot of bother*
Do any of the following upset your asthma? Tick all that apply.	☐ *Colds*	☐ *Strenuous activity or exercise*	☐ *Allergies eg cats, dogs, pollen*	☐ *Cigarette smoke*	**Please complete other side**

Do you have a preventer inhaler (usually brown, orange, red or purple)? ☐ *Yes* ☐ *No, skip to Section B*

Which statement best describes how you take your regular Asthma treatment. Please tick only one box

☐ *I take it every day* ☐ *I take it some days but others I do not* ☐ *I used to take it, but now I do not* ☐ *I take it only when I have symptoms* ☐ *I never take it*

Please tell us how well you use your preventer inhaler:

"I think my inhaler technique is very poor" ☐ *1* ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐ *6* "I think my inhaler technique is excellent"

About your preventer inhaler:	*Strongly disagree*				*Strongly agree*
I need to take my inhaler(s) regularly for my asthma to be well controlled	☐	☐	☐	☐	☐
I find my inhaler(s) difficult to use	☐	☐	☐	☐	☐
Having to take regular asthma medication worries me	☐	☐	☐	☐	☐
I would prefer to take my asthma medications in a once a day dose	☐	☐	☐	☐	☐

Still about your preventer inhaler:	*Never*				*Always*
I use it only when I feel breathless	☐	☐	☐	☐	☐
I avoid using it if I can	☐	☐	☐	☐	☐
I forget to take it	☐	☐	☐	☐	☐
I decide to miss a dose	☐	☐	☐	☐	☐
I choose to take it once a day	☐	☐	☐	☐	☐

When you use your preventer inhaler:	*Yes*	*No*
Do you feel a sensation at the back of the throat?	☐	☐
Do you sometimes feel a need to cough	☐	☐
Do you feel your medication is deposited at the back of your throat?	☐	☐

Do you experience any of these side effects from your preventer inhaler? Please tick yes or no for each one

	Yes	*No*		*Yes*	*No*
Continual sore mouth/throat	☐	☐	Hoarse voice	☐	☐
Oral Thrush	☐	☐	Abnormal Weight Gain	☐	☐
Bruising	☐	☐	Cough	☐	☐

Section B: Have you had the way you take your inhaler(s) checked in the past 12 months? ☐ *Yes* ☐ *No*

Have you seen a specialist respiratory doctor or nurse outside the practice? ☐ *In the last year* ☐ *More than a year ago* ☐ *Never*

If you have a peak flow meter, please tell us your reading today:

for example: 4 2 0 ☐ *I don't have a peak flow meter*

In the future, would you be willing to participate in further research? ☐ *Yes* ☐ *No*

Practice Ref: Survey Ref:

Dutch HARP questionnaire:

Astma Vragenlijst V9.NL

Neem een paar minuten om de hele vragenlijst in te vullen, volg de instructies bovenaan elke bladzijde.

In de afgelopen 7 dagen:	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10+*
Hoe vaak heeft u uw luchtwegverwijder (meestal blauw) gebruikt?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

In de afgelopen 7 dagen: (kruis één vakje aan voor elke vraag):	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Hoeveel dagen had uw astma / ademhalingsproblemen invloed op uw normale activiteiten (bv. sport, school, werk / huishoudelijk werk)?	☐	☐	☐	☐	☐	☐	☐	☐
Hoeveel nachten bent u wakker geworden door astma / ademhalings klachten (inclusief hoesten)?	☐	☐	☐	☐	☐	☐	☐	☐
Hoeveel dagen heeft u astma / ademhalingsklachten gehad?	☐	☐	☐	☐	☐	☐	☐	☐

In de afgelopen 4 weken:	Ja	Nee	Onzeker
Hoeveel dagen heeft u werk, school, of normale dagelijkse activiteiten niet kunnen doen vanwege uw astma / ademhlaingsproblemen?	☐	☐	☐
Hoeveel nachten bent u wakker geworden door astma/ ademhalingsklachten?	☐	☐	☐
Denkt u dat uw astma u weinig of geen klachten geeft?	☐	☐	☐
In het algemeen: gebruikt u een luchtwegverwijder voor een snelle verlichting van uw astma/ademhalingsklachten?	☐	☐	☐

Zo ja, wat was het hoogste aantal pufjes dat u in één dag nam van dit middel, in de afgelopen 4 weken?	*0*	*1 - 4 puffs*	*5 - 8 puffs*	*9 - 12 puffs*	*Meer dan 12 puffs*
	☐	☐	☐	☐	☐

In de afgelopen 12 maanden:	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10+*
Hoe vaak heeft u een kuur antibiotica of prednison nodig gehad voor verergering van uw astma/ ademhalingsklachten?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
	0	1	2	3	4	5	6	7	8	9	10+
....van deze hoeveel was dat alleen een prednisonkuur?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
....van deze hoeveel was dat alleen een antibioticakuur?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
....van deze hoeveel was dat een prednison **en** antibioticakuur?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Toen u een een kuur van antibiotica of prednison nodig had voor verergering van uw astma/ ademhalingsklachten:

Hoe vaak bent u bij de spoedeisende hulp of ergens geweest anders dan bij uw huisarts voor uw astma/ ademhalingsklachten?	☐ *0*	☐ *1*	☐ *2*	☐ *3*	☐ *4*	☐ *5+*
Hoe vaak bent u daarvoor in het ziekenhuis opgenomen geweest?	☐ *0*	☐ *1*	☐ *2*	☐ *3*	☐ *4*	☐ *5+*

Site Ref: ☐ Survey Ref: ☐

Vul de andere kant

Gebruikt u een ontstekingsremmer (inhalatie corticosteroid bijvoorbeeld symbicort, pulmicort, seretide, fluticason; meestal bruin, oranje, rood of paars)? ☐ *Ja* ☐ *Nee, ga dan naar punt B*

Welke uitspraak omschrijft het beste hoe u uw ontstekingsremmer gebruikt. Gelieve slechts één mogelijkheid aan te kruisen

☐ *Ik gebruik het elke dag* ☐ *Ik gebruik het sommige dagen wel en andere dagen niet* ☐ *Ik gebruikte het medicijn, maar nu niet meer* ☐ *Ik gebruik het alleen als ik klachten krijg* ☐ *Ik heb het nooit gebruikt*

Geef aan, tussen de 2 onderstaande stellingen, hoe goed u uw inhalator gebruikt:

"Ik denk dat mijn inhalatietechniek zeer slecht is" ☐ *1* ☐ *2* ☐ *3* ☐ *4* ☐ *5* ☐ *6* "Ik denk dat mijn inhalatie techniek uitstekend is"

Wanneer u uw inhalator met ontstekingsremmer (corticosteroid , bijv symbicort, pulmicort, seretide, fluticason) gebruikt:

	Ja	*Nee*
Moet u daardoor soms hoesten?	☐	☐
Voelt u soms de behoefte om te hoesten?	☐	☐
Heeft u het gevoel dat uw medicatie is achtergebleven in uw keel?	☐	☐

Is de wijze waarop u uw inhalator (s) gebruikt het afgelopen jaar gecontroleerd? ☐ *Ja* ☐ *Nee*

	Lijst van de huidige long medicatie naam van het product	Begindatum, indien medicatie is gewijzigd of gestart afgelopen jaar	Totaal aantal gebruikte inhalers in het afgelopen jaar
1			
2			
3			
4			
5			

B.

Heeft u paracetamol (merknaam) in het afgelopen jaar gebruikt? ☐ *regelmatig* ☐ *onregelmatig* ☐ *Niet gebruikt*

Heeft u medicijnen die een pijnstillende, koortswerende en ontstekingsremmende werking hebben (bijvoorbeeld ibuprofen, asperine en diclofenac) in het afgelopen jaar gebruikt? ☐ *regelmatig* ☐ *onregelmatig* ☐ *Niet gebruikt*

Heeft u de diagnose van "zure oprispingen/zuurbrand ofwel gastro-esofagaal reflux (GERD) " en / of neemt u een van deze medicijnen (Lansoprazol Lansoprazol-, Omeprazol-Protium, Rabeprazole-Pariet)? ☐ *Ja* ☐ *Nee*

Over roken:

	1-5	*6-10*	*11-15*	*16-20*	*21-30*	*31-40*	*41-50*	*50+*
Als u rookt of heeft gerookt, hoeveel sigaretten rookt(e) u per dag?	☐	☐	☐	☐	☐	☐	☐	☐

Betreffende uw neus:

Heeft u een van deze klachten: jeukende neus, loopneus, verstopte neus of niezen als je niet verkouden bent? ☐ *Nee* ☐ *Af en toe een beetje last van* ☐ *Af en toe veel last* ☐ *De meeste dagen maar dan een beetje last* ☐ *De meeste dagen en dan veel last*

Als u een van deze bovenstaande klachten heeft:

Heeft u nasale corticosteroiden in het afgelopen jaar gebruikt? ☐ *Ja* ☐ *Nee*

Heeft u tabletten met antihistaminica in het afgelopen jaar gebruikt? ☐ *Ja* ☐ *Nee*

Heeft u er bezwaar tegen als we contact met u opnemen bij onduidelijkheden? Zo niet, wilt u hier uw telefoonnummer noteren? _____

Appendix 2

Generic errors

Manoeuvre	Classification	Diskus - variable code	Turbuhaler - variable code	MDI – variable code	MDI and spacer - variable code
Preparation					
Exhales into the inhaler before inhalation	Serious error	Accu_Critical_6	Turbo_Critical_12 Turbo_Critical_44	MDI_Error_4	N/A
Inhalation					
Did not breathe out to empty lungs	Serious error	Accu_Error_5	Turbo_Error_11	MDI_PotentCrit_3	Spacer_PotentCrit_5
Did not have head tilted such that chin is slightly upwards	Potentially serious error	Accu_Error_8	Turbo_Error_14	MDI_Error_7	Spacer_PotentCrit_9
Did not put device in mouth and seal lips around mouth piece	Serious error	Accu_Critical_7	Turbo_Critical_13	MDI_PotentCrit_6	Spacer_Critical_8
Did not inhale through mouth	Serious error	Accu_Critical_12 Accu_Critical_13	Turbo_Critical_18 Turbo_Critical_19	MDI_Critical_12 MDI_Critical_13	Spacer_Critical_15 Spacer_Critical_16
No breath-hold (or holds breath for less than 3 seconds)	Potentially serious error	Accu_Error_14	Turbo_Error_20	MDI_Error_14	Spacer_Critical_17
Second dose					
Second dose within 30 seconds	Potentially serious error	Accu_Error_15	Turbo_Error_21	MDI_Error_16	Spacer_Error_19
Did not repeat the second inhalation, if needed	Potentially serious error	Accu_PotentCrit_16	Turbo_PotentCrit_22	MDI_PotentCrit_17	Spacer_Data_Clarify_20
After last inhalation does not replace cap/cover	Potentially serious error	Accu_PotentCrit_31	Turbo_Critical_40	MDI_Error_32	Spacer_Data_Clarify_47
General Knowledge					
Patients' cannot tell whether their inhaler is empty	Potentially serious error	Accu_Critical_32	Turbo_Critical_41	MDI_Critical_33	Spacer_Data_Clarify_36
Patients' has expired inhaler	Serious error	Accu_PotentCrit_33	Turbo_PotentCrit_42	MDI_PotentCrit_34	Spacer_Error_37

Diskus specific errors

Manoeuvre	Classification	Variable code
Preparation		
Did not remove cap/slide cover fully open	Serious error	Accu_Critical_1 Accu_Critical_2
Lost dose after preparation due to shaking or tipped device	Serious error	Accu_Critical_3 Accu_Critical_4
Inhalation		
Inspiratory effort, (inhalation is not fast, forceful from the start and as long as possible)	Potentially serious error	Accu_PotentCrit_9 Accu_Critical_10 Accu_PotentCrit_11
General Knowledge		
None		

DPI Turbuhaler specific errors

Manoeuvre	Classification	Variable code
Preparation		
Did not remove cap or shook Turbuhaler during preparation	Serious error	Turbo_Critical_3 Turbo_Critical_5
Twist errors (Device not held upright, base not twisted until it clicks or turn back to original position)	Serious error	Turbo_Critical_6 Turbo_Critical_7 Turbo_Critical_8
Dose lost after preparation due to shaking or tipping	Serious error	Turbo_Critical_9 Turbo_Critical_10
Inhalation		
Inhalation effort (inhalation not fast, forceful from the start and as long as possible)	Potentially serious error	Turbo_Critical_15 Turbo_Critical_16 Turbo_PotentCrit_17
General Knowledge		
None		

MDI specific errors

Manoeuvre	Classification	Variable code
Preparation		
Did not remove cap	Serious error	MDI_Critical_1
Did not shake before actuation	Serious error	MDI_Error_2
Did not hold inhaler upright	Serious error	MDI_Critical_5
Did not actuate	Serious error	MDI_Critical_11
Inhalation		
Did not coordinate actuation with inhalation; actuation before inhalation	Serious error	MDI_Critical_8
Did not coordinate actuation with inhalation; actuation is too late	Potentially Serious error	MDI_Critical_9
Inspiratory effect - does not inhale slowly and deeply - defined as at least 3 seconds	Potentially serious error	MDI_PotentCrit_10
Coughs during inhalation	Serious error	MDI_Data_Clarify_15
General Knowledge		
If on Fostair – knowing that inhaler can only be used for up to 20 weeks/5 months	Serious error	MDI_PotentCrit_35
Did not mention priming when asked: What do you do when you haven't used your inhaler for: Evohaler, 1 week; or Fostair, 2 weeks?	Potentially serious error	MDI_PotentCrit_37
Did not mention priming when asked: What do you do when you use your inhaler for the first time?	Potentially serious error	MDI_PotentCrit_38

MDI with spacer specific errors

Manoeuvre	Classification	Variable code
Preparation		
Did not correctly assemble the spacer and MDI together	Serious error	Spacer_Error_1 Spacer_Critical_2 Spacer_Error_3 Spacer_Critical_4
Did not hold spacer with inhaler upright	Serious error	Spacer_Critical_6
Did not actuate a dose into the spacer	Serious	Spacer_Critical_7 Spacer_Critical_14
Inhalation		
Did not start to inhale through mouthpiece 2 seconds after actuating one dose	Serious error	Spacer_Critical_10 Spacer_Error_25 Spacer_Critical_28
Inspiratory effect (Did not inhale slowly, steady and deeply - defined as at least 3 seconds (may use tidal breathing this should be slow and relaxed [not panting]), Aerochamber whistles during inhalation)	Serious error	Spacer_PotentCrit_11 Spacer_PotentCrit_13
Coughs during the inhalation	Serious error	Spacer_Critical_18
General Knowledge		
If on Fostair – knowing that inhaler can only be used for up to 20 weeks/5 months	Serious error	Spacer_Critical_38
Does not mention priming when asked: What do you do when you haven't used your inhaler for: Evohaler, 1 week; or Fostair, 2 weeks?	Potentially serious error	Spacer_PotentCrit_40
Did not mention priming when asked: What do you do when you use your inhaler for the first time?	Potentially serious error	Spacer_Data_Clarify_41
Spacer has any faulty parts, valves, or cracks in the plastic	Serious error	Spacer_Critical_44
Error made with washing the spacer	Serious error	Spacer_PotentCrit_48 Spacer_PotentCrit_49 Spacer_Critical_50 Spacer_Critical_51

Appendix 3

Example of the demographics results tables

		GINA asthma control				
		Controlled N=x	Partly controlled N=x	Un-controlled N=x	Total N=x	p-value[a]
Age (years)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Age* categorised, n(%)	16-40 years 41-60 years ≥61 years	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	X
	Total	x (x)	x (x)	x (x)	x (x)	
Gender, n (%)	Male Female	x (x) x (x)	x (x) x (x)	x (x) x (x)	x (x) x (x)	X
	Total	x (x)	x (x)	x (x)	x (x)	
Year of iHARP review	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
BMI, (kg/m^2)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
BMI (categorised), n (%)	Underweight Normal Overweight obese	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x)	X
	Total	x (x)	x (x)	x (x)	x (x)	
Percent predicted peak flow readings (%)*	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Time taken to 90% of inhalation flow	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Year of asthma diagnosed	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Age at asthma diagnosis	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Duration of asthma (years)	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Smoking status*, n (%)	Non-smoker Current smoker Ex-smoker	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	X
	Total	x (x)	x (x)	x (x)	x (x)	
Pack years	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x
Highest education level[*Error! Bookmark not defined.] (categorised), n (%)	Post graduate degree First university degree Any other post-secondary training Completed secondary education Some secondary education Completed primary education Some primary education None	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x) x (x) x (x) x (x)	X
	Total	x (x)	x (x)	x (x)	x (x)	
Country in which the iHARP review took place	Australia England France	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	X

* At iHARP review date

	Holland	x (x)	x (x)	x (x)	x (x)	
	Italy	x (x)	x (x)	x (x)	x (x)	
	Norway	x (x)	x (x)	x (x)	x (x)	
	Spain	x (x)	x (x)	x (x)	x (x)	
	Sweden	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	

[a] P values will be calculated using the following tests: chi square test for categorical variables and ANOVA for variables measured on the interval scale

Example of the co-morbidities and medications results tables

		GINA asthma control				
		Controlled N=x	Partly controlled N=x	Uncontrolled N=x	Total N=x	p-value[a]
Charlson comorbidity index, n (%)	0	x (x)	x (x)	x (x)	x (x)	X
	1-4	x (x)	x (x)	x (x)	x (x)	
	5+	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
Rhinitis severity*, n (%)	No rhinitis	x (x)	x (x)	x (x)	x (x)	X
	Mild rhinitis	x (x)	x (x)	x (x)	x (x)	
	Significant rhinitis	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
GERD treatment†, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	X
	No	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
Cardiac treatment†, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	X
	No	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	

[a] P values will be calculated using chi square test

* Patients with rhinitis identified by asking the following question: Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold? Where the answers could be:

1. No
2. Occasionally and little bother
3. Occasionally and quite a bother
4. Most days and little bother
5. Most days and a lot of bother

Classified by:

No rhinitis: 0

Mild Rhinitis = 1 or 3.

Significant rhinitis = 2 or 4

† In the year prior to the iHARP review

Example of treatment adherence and asthma control results tables

		GINA asthma control				
		Controlled N=x	Partly controlled N=x	Uncontrolled N=X	Total N=x	p-value[a]
MARS score[*]	Good	x (x)	x (x)	x (x)	x (x)	X
	Borderline	x (x)	x (x)	x (x)	x (x)	
	Poor	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
Admission to hospital with asthma related problems[†]	None	x (x)	x (x)	x (x)	x (x)	X
	1-2	x (x)	x (x)	x (x)	x (x)	
	>2	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
A&E (or other none GP) treatment for asthma**Error! Bookmark not defined.**	None	x (x)	x (x)	x (x)	x (x)	X
	≥1	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
Number of course of oral steroids for worsening asthma (exacerbations) **Error! Bookmark not defined.**	None	x (x)	x (x)	x (x)	x (x)	X
	1	x (x)	x (x)	x (x)	x (x)	
	≥2	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	
Inhaler devise	Diskus	x (x)	x (x)	x (x)	x (x)	X
	Turbuhaler	x (x)	x (x)	x (x)	x (x)	
	MDI	x (x)	x (x)	x (x)	x (x)	
	MDI with spacer	x (x)	x (x)	x (x)	x (x)	
	Total	x (x)	x (x)	x (x)	x (x)	

[a] P values will be calculated using chi square test

[*] MARS adherence was reported using the Medication Adherence Rating Scale (MARS) score. This measures adherence on a 6-point scale (never, rarely, sometimes, regular, often and always) in response to the following questions about their preventer inhaler use:

1. I use it only when I feel breathless
2. I avoid using it if I can
3. I forget to take it
4. I decide to miss a dose
5. I choose to take it once a day

Adherence was categorised as: poor (any of the questions answered with 'often' or 'always'), borderline (more than one questions with 'sometimes') and good (none of above).

[†] In the year prior to the iHARP review

Example of additional analysis for UK patients (part 1)

		GINA asthma control				
		Controlled N=x	Partly controlled N=x	Un-controlled N=x	Total N=x	p-value[a]
Prescribed ICS dose (mcg)[*]	N (% non-missing) Mean (SD) Median (IQR)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	x (x) x (x) x (x, x)	X
Number of prescription for any respiratory therapy in previous year, n (%)	0 1-5 5-10 >10 Total	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	x (x) x (x) x (x) x (x) x (x)	X
Change in therapy[†]	Stable Unstable Total	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	x (x) x (x) x (x)	X
SABA prescriptions[‡] (categorised)	None, n (%)	x (x)	x (x)	x (x)	x (x)	X
	1, n (%)	x (x)	x (x)	x (x)	x (x)	
	2, n (%)	x (x)	x (x)	x (x)	x (x)	
	3-4, n (%)	x (x)	x (x)	x (x)	x (x)	
	5+, n (%)	x (x)	x (x)	x (x)	x (x)	
SABA inhalers (categorised)	None, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1, n (%)	x (x)	x (x)	x (x)	x (x)	
	2, n (%)	x (x)	x (x)	x (x)	x (x)	
	3-4, n (%)	x (x)	x (x)	x (x)	x (x)	
	5+, n (%)	x (x)	x (x)	x (x)	x (x)	
SABA dosage (mcg) (categorised)	None, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1-100, n (%)	x (x)	x (x)	x (x)	x (x)	
	101-200, n (%)	x (x)	x (x)	x (x)	x (x)	
	201-400, n (%)	x (x)	x (x)	x (x)	x (x)	
	401-800, n (%)	x (x)	x (x)	x (x)	x (x)	
	801 +, n (%)	x (x)	x (x)	x (x)	x (x)	

[a] P values will be calculated using the following tests: chi square test for categorical variables and ANOVA for variables measured on the interval scale

[*] At iHARP review date

[†] Unstable: ≥50% increase in ICS dose, additional therapy or switch to a different therapy in the same class, Stable: all others

[‡] Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in mcg); (Number of inhalers*doses per inhaler)/365*strength and categorised as appropriate to the data.

Example of additional analysis for UK patients (part 2)

		GINA asthma control				
		Controlled N=x	Partly controlled N=x	Un-controlled N=x	Total N=x	p-value[a]
Antibiotics script with evidence of respiratory consultation [*](categorised)	0, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1, n (%)	x (x)	x (x)	x (x)	x (x)	
	2+, n (%)	x (x)	x (x)	x (x)	x (x)	
Beta blockers[†]	No, n (%)	x (x)	x (x)	x (x)	x (x)	x
	Yes, n (%)	x (x)	x (x)	x (x)	x (x)	
NSAIDs[†]	No, n (%)	x (x)	x (x)	x (x)	x (x)	x
	Yes, n (%)	x (x)	x (x)	x (x)	x (x)	
Asthma Consultations (Categorised)[‡]	0, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1, n (%)	x (x)	x (x)	x (x)	x (x)	
	2+, n (%)	x (x)	x (x)	x (x)	x (x)	
Non Asthma related consultations‡ (categorized)	0-2, n (%)	x (x)	x (x)	x (x)	x (x)	x
	3-4, n (%)	x (x)	x (x)	x (x)	x (x)	
	5-6, n (%)	x (x)	x (x)	x (x)	x (x)	
	7-9, n (%)	x (x)	x (x)	x (x)	x (x)	
	10+, n (%)	x (x)	x (x)	x (x)	x (x)	
Asthma-related inpatient admissions[§] (Categorised)	0, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1+, n (%)	x (x)	x (x)	x (x)	x (x)	
Asthma-related A&E attendance	0, n (%)	x (x)	x (x)	x (x)	x (x)	x
	1+, n (%)	x (x)	x (x)	x (x)	x (x)	

[a] P values will be calculated using the following tests: chi square test for categorical variables and ANOVA for variables measured on the interval scale

[*] Evidence of a Respiratory Review - consists of the following: Any Lower Respiratory Consultation (see above) and any additional respiratory examinations, referrals, chest x-rays or events.

[†] >=1 prescriptions during the year prior to the iHARP review

[‡] In the year prior to the iHARP review

[§] Asthma-related hospitalisations - consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation read code which has been recorded on the same day as a Lower Respiratory Consultation (see below; (a) – (c))

A lower Respiratory Consultations - consist of the following: a) Lower Respiratory read codes (including Asthma, COPD and LRTI read codes); b) Asthma/COPD review codes excl. any monitoring letter codes; c) Lung function and/or asthma monitoring; d) Any additional respiratory examinations, referrals, chest x-rays or events

Example table of generic device errors

Manoeuvre		Diskus	Turbu-haler	MDI	MDI and spacer	Total
Preparation						
Does not remove cap/slide cover fully open, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Inhalations						
Does not breathe out to empty lungs, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Does not have head tilted such that chin is slightly upwards, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Does not inhale, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Inhales through the nose, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
No breath-hold (or holds breath for less than 3 seconds), n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Second does within 30 seconds, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Does not repeat the second inhalation, if needed, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
After last inhalation does not replace cap/cover, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
General knowledge						
Patients' has expired inhaler, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Patients' cannot tell whether their inhaler is empty, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)
Patients' did not bring their own inhaler to the clinic, n (%)	Yes	x (x)	x (x)	x (x)	x (x)	x (x)
	No	x (x)	x (x)	x (x)	x (x)	x (x)
	Total	x (x)	x (x)	x (x)	x (x)	x (x)

Example table of devise specific errors

Diskus		Total
Preparation		
Shakes Diskus inhaler after dose preparation, n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
Holds inhaler in a downward position after dose preparation (before inhalation), n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
Inhalations		
Exhales into the inhaler before inhalation, n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
Inhalation is not fast, forceful from the start and as long as possible, n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
Does not put inhaler in mouth and seal lips around mouthpiece, n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
No breath-hold (or holds breath for less than 3 seconds), n (%)	Yes	x (x)
	No	x (x)
	Total	x (x)
General knowledge		
None		

Example table of the primary outcomes – GINA asthma control status

	Asthma Control Status – GINA				Odds Ratio (95% CI)	
	Controlled n (%)	Partly controlled n (%)	Uncontrolled n (%)	Total, n (%)	Controlled vs partly controlled vs uncontrolled	p-value[a]
Does not remove cap/slide cover fully open (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not breathe out to empty lungs (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not have head tilted such that chin is slightly upwards (Yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not inhale (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Inhales through the nose (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
No breath-hold (or holds breath for less than 3 seconds) (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Second does within 30 seconds (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not repeat the second inhalation, if needed (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
After last inhalation does not replace cap/cover (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' has expired inhaler (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' cannot tell whether their inhaler is empty (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' did not bring their own inhaler to the clinic (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x

[a]Chi squared

Example table for the results of the multivariate analysis

	Asthma Control Status – GINA				Adjusted[a] Odds Ratio (95% CI)	
	Controlled n (%)	Partly controlled n (%)	Uncontrolled n (%)	Total, n (%)	Controlled vs partly controlled vs uncontrolled	p-value[b]
Does not remove cap/slide cover fully open (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not breathe out to empty lungs (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not have head tilted such that chin is slightly upwards (Yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not inhale (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Inhales through the nose (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
No breath-hold (or holds breath for less than 3 seconds) (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Second does within 30 seconds (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Does not repeat the second inhalation, if needed (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
After last inhalation does not replace cap/cover (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' has expired inhaler (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' cannot tell whether their inhaler is empty (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x
Patients' did not bring their own inhaler to the clinic (yes)	x (x)	x (x)	x (x)	x (x)	x (x,x)	x

[a] Adjusted for potential confounders, [b] Conditional Logistic regression