Characterising patients at risk of failed Diskus use in primary care

An example protocol for how to use the iHARP dataset

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A Research in Real Life Study Protocol developed on behalf of Teva Pharmaceuticals

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Objectives

1. Define the serious errors commonly performed by patients with asthma using Diskus (refer to Table 1 and Appendix A)
2. Characterise patients who perform serious errors using Diskus and those that do not
3. Examine patient reported outcomes with Diskus usage

The above objectives will enable the relationship between inhalation technique and clinical outcomes to be investigated.

Background

Asthma is one of the most common chronic diseases, with an estimated 300 million sufferers worldwide and affecting around 6% of the population in the European Union [1]. In addition to its effect on quality of life (both patients and caregivers) it represents a considerable financial burden to society, through direct medication costs and those arising from emergency treatment [2]. A recent European study suggested that over 50% of patients with asthma are sub-optimally controlled [3].

Bronchodilators and inhaled corticosteroids (ICS) are the cornerstone of asthma treatment. There have been many delivery systems developed with no significant differences in outcome [4] but each with advantages and disadvantages [5,6]. Among these, the most frequently used devices are the metered-dose inhalers (MDIs), breath-actuated metered-dose inhalers (BAIs) and dry powder inhalers (DPIs). Correct handling of these devices is crucial for efficient therapy. Effective use of inhalers requires proper inhalation technique.

Correct use of inhalation devices is an inclusion criterion for all studies comparing inhaled treatment and their outcome. In real life, however, the misuse of inhalers has been observed to be common in clinical practice, ranging from 10-85% [7], and is associated with poor clinical outcomes such as reduced bronchodilation and decreased disease control in asthmatics referring to chest clinics [8].

DPIs were introduced as user-friendly devices. Being breath-actuated, DPIs overcome the difficulties in co-ordinating inhaler actuation and inspiration, one of the most common errors made with MDIs [6]. The Diskus DPI is one such device designed to facilitate easy use and patient acceptance. In 1999, van der Palen et al [7] concluded that the Diskus inhaler seems to be the most fool-proof device. However, a review [6] has shown that misuse of DPIs is also common in real life, especially in older patients [8]. Several recent meta-analyses showed that any of the inhaler device types can be equally effective in treating patients [9-11]. The primary qualifications are that the patient is able to use the device correctly and that the drug is available in the device.

There are suggestions that patients with serious breathing impairment, such as during an exacerbation, would not be able to generate the flows and volumes required for adequate inhalation of a DPI [12]. However, in a 2004 study [13], Broeders et al concluded that during an exacerbation, patients gave optimum outcomes with Diskus compared to a volumatic or MDI.

Finally, it is well known that a patient's preference for an inhaler device is associated with ease of inhaler instructions as well as increased likelihood of correct use [14, 15]. This suggest that patient

characteristics are an important predictive factor associated with inhaler misuse that may impact on patient outcomes.

The iHARP review service implements the goals of the International Primary Care Respiratory Group's (IPCRG) Helping Asthma in Real Patients initiative (HARP). This is achieved by analysing inhaler use in iHARP patients reviewed since June 2011 across the world. Based on this data, we wish to evaluate the frequency and characteristics of serious inhaler errors performed by patients in routine care.

The aim of this study is to identify patient characteristics in a large sample of primary care patients that use a Diskus inhaler. The prevalence and factors associated with inhaler misuse will be investigated. In addition we aim to assess the relationship between inhalation technique and clinical outcomes. These results should assist physicians in evaluating the potential impact of the type of device prescribed to a patient.

Research Questions

This study will answer the following questions:

- Which serious errors in Diskus inhaler technique are most frequently made?
- Are certain patient characteristics linked to incorrect inhaler technique for Diskus?
- Are patient reported outcomes linked to incorrect inhaler technique for Diskus?
- Does incorrect inhaler technique correlate to asthma risk assessment?

In addition, the type and frequency of serious errors being performed when using Diskus will be analysed to better characterise patient errors and identify ways in which inhaler technique may be improved.

Methods

Study design and data source

This study will be a retrospective, observational, database analysis using the iHARP dataset. The iHARP dataset is a unique international dataset comprising anonymised data from practices receiving the iHARP asthma review.

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 report were last updated on 5 November 2013.
Several types of anonymised data are typically collected:

1. **Routine clinical data:** Optimum Patient Care (OPC) software interfaces with primary care practice management systems and extracts anonymised, patient-level diagnostic, clinical and prescribing information
2. **Clinician reviews:** Including patient reported data: symptoms, smoking status, comorbidity, treatment, adherence, subjective and objective inhaler technique, results, lung function, NiOX readings

iHARP International dataset:

Patients were recruited from the UK, the Netherlands and other countries as a group (Global): Norway, Spain, Italy, Sweden, Australia and France. Appendix B details the English and Dutch questionnaires and Appendix C details the iHARP database service specification.

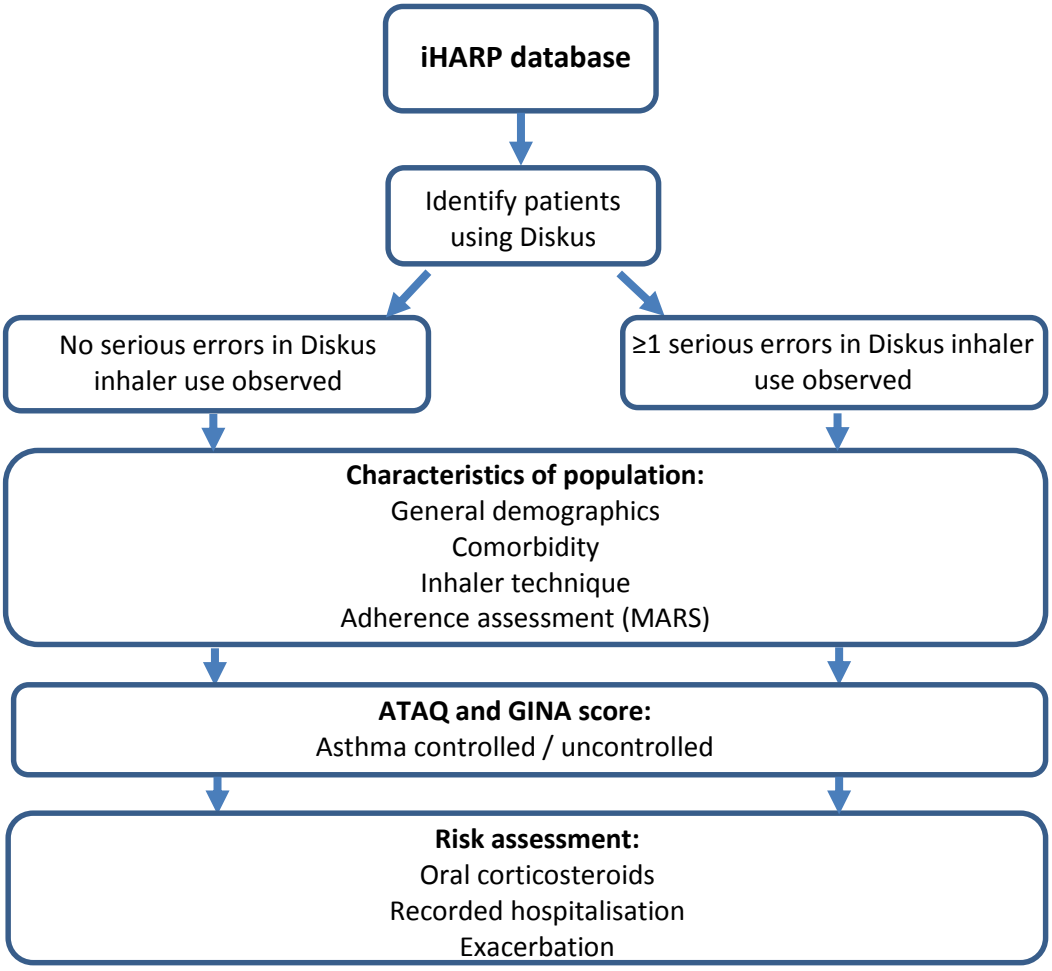

Figure 1. Overview of study design

Study population

Inclusion criteria:

Patients invited to participate in iHARP should meet the following inclusion/exclusion criteria:

- Adults (aged ≥ 18 years)
- Current diagnosis of asthma (Step 3 or 4 of Global Initiative for Asthma [GINA] guidelines)
- Receiving current asthma therapy as fixed dose combination (FDC) inhalation corticosteroids (ICS) in combination with long-acting beta agonist (LABA) by using a Diskus device
- iHARP review performed by a clinician
- Agreement with the practice for using the anonymous data for research objectives

In addition, for this analysis patients must have been:

- Prescribed Diskus for regular/preventer asthma therapy

Exclusion criteria:

- Age ≤ 17 years
- Diagnosed with COPD

Patient evaluations

The following steps outline the processes undertaken to define the characteristics of patients who are using Diskus, which in turn provides an overview of the study population.

Step 1: Define serious errors

Patients will be separated into two groups: those performing serious error(s) and those that do not. Only serious errors will be used; potentially serious errors will not be included as there is no evidence for a reduced medication uptake with these type of errors.

Table 1 lists the serious and potentially serious errors that will be used to assess Diskus inhaler technique in this study. Refer to Appendix A for a full list of serious and potential error for other devices, approved by the steering committee in December 2013.

Table 1: Checklists used to assess inhaler technique of DPI Diskus

Serious errors:	**Potentially serious errors:**
Dose preparation:	**Dose preparation:**
Does not slide cover as far as possible	Does not slide cover back after inhalation
Does not slide lever fully	
Manoeuvre:	**Manoeuvre**:
Holds in a downward position after dose preparation	Failure to tilt head with chin slightly upwards
Shakes after dose preparation	Inhalation is not as fast as you can
Failure to exhale away from mouthpiece	Inhalation is not as long as you can
Does not breath out slowly to residual volume	Not repeating the second inhalation
Failure to put in mouth and seal lips around mouthpiece	If second dose required: second dose within 30 sec
Failure to inhale through mouthpiece	Patient has expired device
Inhalation through the nose	
Inhalation is not forceful from the start	
No breath-hold for at least 3 seconds	
Does not prepare second dose as above	
Does not correctly inhale second dose as above.	
Patient does not know when their device is empty	

Step 2: Describe the patient demographics

Perform statistical analysis (see below) for the following variables:

Table 2. A selection of variables used in the study (please see appendix D for syntax used for some additional variables)

Demographics	iHARP database variable	New variable, made in SPSS	Comments
Gender	Gender		
Age	Age	Age_cat	18-30, 31-50, 51-70, ≥71
BMI	BMI	BMI_cat	Underweight (< 18.5), Normal BMI (18.5 - 24.99), Overweight (25-29.99), Obese (≥30)
Education	EducID		0-8: Post graduate or professional degree, first university degree, any other post-secondary training, completed secondary education, some secondary education, completed primary education, some primary education, none, unknown
Country	Country		
Smoking state	Q_smoke		0-2: never, current, ex-smoker.
Rhinitis	Q_rhinitis	Rhinitis_Yes_No	Yes/No
Severity Rhinitis	Q_rhinitis	Rhinitis_Cat	Classified as below[a]
Charlson comorbidity index	ConTissue till metastatic tumor	Charlson_Cat	See figure 3, for point system. Categorise in: 0,1,2, ≥3
Duration of diagnose	Age_at_diagnosis	New_Age_Diagnose Age_at_diagnosis_Cat	New_Age_Diagnose = a combination of Age_at_diagnosis and Year_of_diagnosis. If Age_at_diagnose is missing,

[a] 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

			then calculated by Age-(2012-Year of diagnose) Categories: 0-17, 18-30, 31-50, 51-70, >70
Duration of Diskus use	Age_at_diagnosis	Duration_of_diagnosis	Age – Age_of_diagnosis
PEF	Q_PEF1, Q_PEF2, Q_PEF3,	See syntax for GINA score: Best_PEF_Male, Best_PEF_Female	
FEV1	A_FEV1_reading	See syntax for GINA score: Best_FEV1_Male, Best_FEV1_Female	
%PEF/FEV1	See syntax GINA score	Ratio_PEF_ FEV1_Cat3	Categorise as >0.8, 0.6-0.8, <0.6

Please see appendix D for syntax used for some additional variables.

Charlson Comorbidity Index

The Charlson comorbidity index, based on the ICD-9, predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3 or 6 (see table 3). In this study, the score will be used to classify comorbidities, and will not be used for predicting the ten-year mortality. In addition, we will not include points for every decade >40 years and will calculate the predicted ten-year survival with a specific value.

Table 3: Charlson Comorbidity Index Scoring System:

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumour without metastases (exclude if >5 y form diagnosis)
	Leukemia (acute or chronic)
	Lymphona
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AIDS (not just HIV positive)

Lung function:

For Peak Expiratory Flow (PEF) readings, please note BEST_PEF is provided by the patient, whereas other PEF measurements (termed Q_PEF1, Q_PEF2 and Q_PEF3 in the dataset) are taken at the iHARP review. For this analysis we use the three readings taken at the iHARP review for calculating lung function for that particular timeframe and also for the asthma outcome (see next below, GINA score).

Step 3: Inhaler technique

All patients are asked if their inhaler technique had been checked in the last 12 months. They also report their own subjective technique assessment by using a quantified Likert scale with scores of 1 to 6, where 1 corresponds to "I think my inhaler technique is very poor" and 6 to "I think my inhaler technique is excellent".

The objective evaluation is performed by the clinician from the evaluation of technique using the serious error list (see table 1).

The frequency of each error will be documented to determine which are most frequently observed.

Table 4: Description of variables used for patient inhaler technique

Inhaler technique	iHARP database variable	New variable, made in SPSS	Comments
Inhaler Check	Q_Inh_Check		
Subjective inhaler technique	Q_Inh_Tech		
AIMs	pif	PIF_Cat	PIF ≥60L/min = good, 31-59L/min = suboptimal, ≤30L/min = bad
Which Error	Accu_Critical1 to Accu_potentialCritical33		

Inhalation technique by acceleration:

Good inhalation acceleration is thought to be necessary for a good deposition of medication to the lungs. For this reason we will measure acceleration using the following two methods:

1. Subjective: patient answers yes or no to the following:
    a. Do you feel a sensation at the back of the throat?
    b. Do you feel a need to cough?
    c. Do you feel your medication is deposited at the back of your throat?
2. Objective: Clinician will evaluate acceleration by either:
    a. Spirotrac: Measurement of Peak Inhalation Flow (PIF) and Inhalation Volume (IV)
    b. AIMS (Aerosol Inhalation Monitor) assessment of acceleration: PIF > 60L/min is good; 31-59 L/min = suboptimal, < 30 L/min is bad

Step 4: Adherence assessment

Adherence will be patient 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: Low (any of the questions answered with 'often' or 'always'), borderline (more than one questions with 'sometimes') and good (none of above).

Note: the Dutch population have only one question instead of the MARS. Patients were asked if they sometimes forget their medication on a 6-point scale, where 'never' or 'rarely' indicates good adherence, 'now and then' and 'regularly' will be borderline adherence, and 'very often' and 'always' are defined as low adherence.

Table 5: Description of methods for assessing patient adherence

Adherence item	iHARP database variable	New variable, made in SPSS	Comments
MARS score	Adherence (Using Q_MARS1-Q_MARS5)		1-3 = Good, Borderline, Low
Dutch Adherence	Dutch_Adherence_Result		1-3 = Good, Borderline, Low

Step 5: Patient evaluation of asthma control

The level of clinical asthma control is defined according to symptoms and the degree to which asthma impairs an individual's day-to-day activities and quality of life. Measures that are used to quantify asthma symptoms in primary care are daytime and night-time symptoms, reduced activities, level of short acting β2 agonist reliever usage and impaired lung function.

Table 6: Description of methods for patient evaluation of asthma control

Evaluation item	iHARP database variable	New variable, made in SPSS	Comments
GINA score	Q_Reliever, Q_RCP_activity, Q_RCP_Nights, Q_RCP_symptoms Q_PEF1, Q_PEF2, Q_PEF3, Q_FEV1_reading	GINAscore_ New_Cat	See below for explanation & Appendix D for syntax. 0 = controlled, 1 = partly controlled 2 = uncontrolled UK and global use PEF. Dutch data use FEV1.
ATAQ score	Q_ATAQ1a, Q_ATAQ1b, Q_ATAQ1c, Q_ATAQ2 all summarised in ATAQ_score	ATAQ_Cat	See Appendix B for the questionnaire to facilitate the calculation to score for ATAQ. (ATAQ2 was NOT available for Global data till June 2013)

GINA score:

The GINA score is based on the following calculation: One point for each item:

- RCPActivities > 0 (asthma interfered with normal daily activities at least once in the last week)
- RCPNights > 0 (affected / woken by asthma symptoms at least once in the last week)
- RCPSymptoms > 2 (experienced asthma symptoms at least three times in the last week)
- Reliever > 2 (used reliever inhaler at least three times in the last week)
- bestPEF / predictedPEF < 0.8 (peak expiratory flow is less than 80% of predicted)
  Where the predicted PEF has to been calculated by the following:
  - if male: predictedPEF = ((5.317 * height) - (0.062 * age) + 3.884) * 60;
  - if female: predictedPEF = ((4.087 * height) - (0.050 * age) + 2.945) * 60
    Use FEV1 when PEF is not available.
  - If male: Predicted FEV_1 = 4.30*height{metres} - 0.029*age{years} - 2.49
  - If female: Predicted FEV_1 = 3.95*height{metres} - 0.025*age{years} - 2.60

GINA score is associated with the following control status definitions:

0: controlled
1 to 2: partly controlled
3+: uncontrolled

Asthma Therapy Assessment Questionnaire (ATAQ) score:

ATAQ score is calculated using the asthma therapy assessment questionnaire (see Appendix B - only the light blue parts are available in the iHARP database).

From June 2011 – June 2013 ATAQ2 was not available for the global data. Therefore we extrapolated this value from the Q_reliever question. A receiver operating characteristic (ROC) curve was developed (see Appendix E) to calculate what the most reliable prediction would be. This is summarised below:

If q_reliever = 0-4 or 7 then the ATAQ_2 = 0-4 puffs, adding 0 points to the ATAQ score.
If q_reliever = 5-6 or 8+ then the ATAQ_2 = 5+, adding 1 point to the ATAQ score.

Please see Appendix D for syntax for predicting Q_ATAQ2 from Q_reliever.

Step 6: Patient evaluation by risk assessment

Asthma control should reflect the minimisation of future risk of exacerbation or disease progression. To differentiate patients in certain levels of risk assessment we used the frequency of exacerbation in the prior year.

Severe exacerbations were patient-reported on iHARP questionnaires, with health care professionals asking the following question: “How many exacerbations for asthma did the patient have in the year preceding today?”
Exacerbations were categorised as follows:

- Patients having had ≥2 exacerbations in the year prior
- Patients having had 1 exacerbation in the year prior
- Patients having had 0 exacerbations in the year prior

In addition, asthma-related hospitalisations and acute courses of oral steroids were recorded.

Asthma-related hospitalisations were defined as either or both of the following in the year prior to the asthma review: (1) an asthma-related in-patient admission; or (2) an asthma-related A&E visit. Asthma-related hospitalisations were patient-reported on iHARP questionnaires.

The number of acute courses of oral steroids in the year before the asthma review were patient-reported on iHARP questionnaires.

Table 7: Description of methods for patient evaluation of risk assessment

Evaluation item	iHARP database variable	New variable, made in SPSS	Comments
Oral steroids use in last 12 months	Q_steroids	Steroids_Cat	Categorised as: 0,1,2, ≥3
Admission hospital OR A&E visit last 12 months	Q_Hosp_Admit, Q_Accid_Emerg	Hosp_OR_AE, Hosp_OR_AE_Cat	Added together, then categorised as: 0,1,2, ≥3
Exacerbations in last 12 months	Q_steroids Q_Hosp_Admit Q_Accid_Emerg	Exacerbation Exacerbation_cat	Added together, then categorised as: 0,1,≥2 0 = low, 1 = moderate, ≥2=high risk.

Statistical analysis

General

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p<0.10$.
All analyses were carried out using SPSS version 19 and 21 (IBM SPSS Statistics, Feltham, Middlesex, UK), SAS version 9.3 (SAS Institute, Marlow, Buckinghamshire, UK), and Microsoft Excel software (Microsoft Corporation, Redmond, Washington, US).

Summary statistics

Part I: Characteristics

Summary statistics were produced for all variables, as a complete dataset and by error categories analysed. For variables measured on the interval or ratio scale, these include:

- Sample size
- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile range (25th and 75th percentiles)

For categorical variables, the summary statistics include:

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

Demographic characteristics and measures of disease severity were compared using the Mann-Whitney U test for numeric variables and the $\chi 2$ test for categorical variables.

The influence of patient characteristics on serious errors was evaluated by comparing the percentage of patients with no serious errors with the percentage of patients having at least one HCP-observed serious error.

Patients with and without serious errors were categorised by MARS adherence and risk of exacerbations. Comparisons were made using a t-test or Mann-Whitney U test, depending on the distribution of the data, for variables measured on the interval/ratio scale and the $\chi 2$ test for categorical variables.

Part II: Odds of performing errors

Univariable logistic regression models, with a dichotomous indicator variable for serious errors made (yes/no) as the dependent variable and each patient characteristic as an explanatory variable, were first used to identify characteristics associated with making serious errors. Demographic and clinical characteristics associated with making ≥1 serious errors in the univariable model ($P<0.05$) were entered into a multivariable model, which was stepwise reduced to produce a final list of non-collinear independently associated variables.

Variables included in the univariable model: age; sex; BMI; smoking status; age at asthma diagnosis; Charlson Comorbidity Index score; country; education; rhinitis diagnosis; rhinitis severity; duration of asthma; PEF or FEV1 % predicted; patient report of inhaler technique review by HCP; patient self-

assessment of inhaler technique; adherence to asthma therapy; ATAQ control; GINA control; acute courses of oral corticosteroids; asthma-related hospitalisations; severe exacerbations. Variables included in the multivariable model were: sex; BMI; patient report of inhaler technique review by HCP; ATAQ control; and asthma-related hospitalisations.

Discussion

As with all real-life database studies, using the real-life datasets presents a number of limitations for which it will not be possible to fully adjust (e.g., potential confounding by severity for factors indiscernible from patient records or patient reported outcomes). While the methods of matching and statistical modelling described in this protocol will address all factors for which it is possible to account, given the internal validity limitations of database studies, the results should be viewed in conjunction with those of other study designs, in particular RCTs.

Dissemination and communication of study results

As with all work undertaken by this research team, the study will be registered with clinicaltrials.gov and the initial results will aim to be presented in poster 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 aim to be made as soon as the analyses are completed and the results are verified (see the timelines section of the protocol for anticipated publication dates). Preferred respiratory congresses and journals will be agreed in discussion with Teva Pharmaceuticals, as the study sponsor.

Researcher team

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Appendix A: List of serious and potentially serious errors

As approved by the steering committee in December 2013.
Note: If patients require a second dose, all items will be re-evaluated for the second dose.

DPI Diskus

Variable name in iHARP database	Error for DPI Diskus	Classification
Accu_Critical_1	Does not slide cover as far as possible	Serious
Accu_Critical_2	Does not slide lever fully to open mouthpiece	Serious
Accu_Critical_3	Holds in a downward position after dose preparation (before an inhalation)	Serious
Accu_Critical_4	Shakes after dose preparation	Serious
Accu_Error_5	Does not breathe out slowly to empty lungs to residual volume	Serious
Accu_Critical_6	Exhales into the device	Serious
Accu_Critical_7	Fails to put in mouth and seal lips around mouthpiece	Serious
Accu_Error_8	Failure to tilt head with chin slightly upwards	Potentially serious
Accu_PotentCrit_9	Inhalation is not as fast as you can (defined as a very fast suck)	Potentially serious
Accu_Critical_10	Inhalation is not forceful from the start	Serious
Accu_PotentCrit_11	Inhalation is not as long as you can (>3 sec)	Potentially serious
Accu_Critical_12	Failure to inhale through mouthpiece	Serious
Accu_Critical_13	Inhalation through the nose	Serious
Accu_Error_14	No breath-hold (or for less than 3 seconds)	Serious
Accu_Error_15	If second dose required: takes second dose within 30 seconds	Potentially serious
Accu_PotentCrit_16	Not repeating the second inhalation	Potentially serious
Accu_PotentCrit_31	After (second) inhalation: Does not slide cover back	Potentially serious
Accu_Critical_32	Patient doesn't know when their device is empty	Serious
Accu_PotentCrit_33	Patient has an expired device	Potentially serious

DPI Turbohaler

Variable name in iHARP database	Error for DPI Turbohaler	Classification
Turbo_Critical_3	Dose preparation: Does not remove cap	Serious
Turbo_Critical_5	Dose preparation: Shakes during preparation	Serious
Turbo_Critical_6	Doesn't hold device upright (mouthpiece skywards +/- 45°) during dose preparation	Serious
Turbo_Critical_7	Dose preparation: Dose not twist the base until it clicks	Serious
Turbo_Critical_8	Dose preparation: Does not turn it back to the original position	Serious
Turbo_Critical_9	Device not held upright (mouthpiece skywards) after the base is twisted until inhalation (within 90 degrees)	Serious
Turbo_Critical_10	Shakes after dose preparation	Serious
Turbo_Error_11	Does not breathe out slowly to empty lungs to residual volume	Serious
Turbo_Critical_12	Exhales into the device (or blowing into the device before inhalation)	Serious
Turbo_Critical_13	Fails to put in mouth and seal lips around mouthpiece	Serious
Turbo_Error_14	Does not have head tilted such that chin is slightly upwards	Potentially serious
Turbo_Critical_15	Inhalation is not as fast as you can (defined as a very fast suck)	Serious
Turbo_Critical_16	Inhalation is not forceful from the start	Serious
Turbo_PotentCrit_17	Inhalation is not as long as you can, at least 3 seconds	Potentially serious
Turbo_Critical_18	Failure to inhale through mouthpiece	Serious
Turbo_Critical_19	Inhalation through the nose	Serious
Turbo_Error_20	No breath-hold for at least 3 seconds	Serious
Turbo_Error_21	If second dose required: takes second dose within 30seconds	Potentially serious
Turbo_PotentCrit_22	Doesn't repeat the second inhalation, if required	Potentially serious
Turbo_Critical_40	After (second) inhalation does not replace cap	Potentially serious
Turbo_Critical_41	Patients cannot tell when their device is empty	Serious
Turbo_PotentCrit_42	Patient has an expired device	Potentially serious
Turbo_Critical_44*	Blowing into the device before inhalation	Serious*

* Identical to Critical 12. Calculated as follows:
If Turbo_Critical_12 is positive (=1) then there will be a 1 in Turbo_Critical_44. If Turbo_Critical_44 = 1, this will stay 1. Regardless to the outcome of Turbo_Critical_12. For counting total errors, we will only count Turbo_Critical_44.

MDI without spacer

Variable name in iHARP database	Error for MDI without spacer	Classification
MDI_Critical_1	Does not remove cap	Serious
MDI_Error_2	Does not shake before actuation	Serious
MDI_PotentCrit_3	Does not breathe out	Serious
MDI_Error_4	Exhalation into the inhaler	Potentially serious
MDI_Critical_5	Does not hold inhaler upright	Serious
MDI_PotentCrit_6	Puts inhaler in mouth, but does not seal lips	Potentially serious
MDI_Error_7	Does not have head tilted such that chin is slightly upwards	Potentially serious
MDI_Critical_8	Actuation not corresponding with inhalation; actuation before inhalation	Serious
MDI_Critical_9	Actuation not corresponding with inhalation; actuation is too late	Serious
MDI_PotentCrit_10	Inhalation is not slow and deep - defined as lasting at least 3 seconds	Serious
MDI_Critical_11	Failure to actuate	Serious
MDI_Critical_12	Failure to inhale	Serious
MDI_Critical_13	Inhalation through the nose	Serious
MDI_Error_14	No breath-hold for at least 3 seconds	Serious
MDI_Error_16	Second dose within 30 seconds	Potentially serious
MDI_PotentCrit_17	No second inhalation	Potentially serious
MDI_Error_32	After (second) inhalation - doesn't replace cap	Potentially serious
MDI_Critical_33	When asked - patient does not know how to tell that their device is empty	Serious
MDI_PotentCrit_34	Patient has an expired device	Potentially serious
MDI_PotentCrit_35	If on Fostair ask if they know how long they can use their inhaler after receiving it from the pharmacy - should be less than 20 weeks/5 months	Serious
MDI_PotentCrit_37	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
MDI_PotentCrit_38	Does not mention priming when asked: What do you do when you use your inhaler for the first time?	Potentially serious

MDI with spacer

Variable name in iHARP database	Error for MDI with spacer	Classification
Spacer_Error_1	Does not know how to correctly assemble the spacer	Serious
Spacer_Critical_2	Does not remove cap	Serious
Spacer_Error_3	Does not shake before placing into spacer	Serious
Spacer_Critical_4	Does not insert mouthpiece into spacer ensuring a tight seal - there should be a click heard with the volumatic and with the aerochamber it should be inserted with a tight seal and the inhaler should be vertical at 90 degrees	Serious
Spacer_PotentCrit_5	Does not breathe out	Potentially serious
Spacer_Critical_6	Does not hold spacer with inhaler upright	Serious
Spacer_Critical_7	Does not actuate just one dose into the spacer (either no dose actuated or actuates more than one dose)	Serious
Spacer_Critical_8	Put spacer mouthpiece in mouth but does not seal lips	Serious
Spacer_PotentCrit_9	Does not have head tilted such that chin is slightly upwards	Potentially serious
Spacer_Critical_10	Does not start to inhale through mouthpiece within 2 seconds of discharging one dose	Serious
Spacer_PotentCrit_11	Inhalation is not slow, steady and deep - defined as lasting at least 3 seconds (some may use tidal breathing this should be slow and relaxed not panting)	Serious
Spacer_PotentCrit_13	Aerochamber whistles during inhalation	Potentially serious
Spacer_Critical_14	Failure to actuate a dose into the spacer	Serious
Spacer_Critical_15	Failure to inhale	Serious
Spacer_Critical_16	Inhalation through the nose	Serious
Spacer_Critical_17	No breath-hold (or for less than 3 seconds)	Serious
Spacer_Critical_18	Patient coughed during the inhalation	Serious
Spacer_Error_19	Second dose within 30 seconds	Potentially serious
Spacer_Critical_28	Starts to inhaler through mouthpiece within 2 seconds of discharging one dose	Serious
Spacer_Error_37	Patient has an expired device	Potentially serious
Spacer_Critical_38	If on Fostair, ask if they know how long they can use their inhaler after receiving it from the pharmacy - should be less than 20 weeks/5 months)	Serious
Spacer_PotentCrit_39	Patient did not bring their own device to the clinical visit	Potentially serious
Spacer_PotentCrit_40	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
Spacer_PotentCrit_42	Does not mention priming when asked: "What do you do when you haven't used your inhaler for 24 hours? (Evohaler 1 week, Fostair 2 weeks)"	Potentially serious
Spacer_Critical_44	Spacer has any faulty parts, valves, or cracks in the plastic	Serious
Spacer_Critical_48	Does not wash in soapy /detergent water at least once a week	Serious
Spacer_PotentCrit_49	Rinses only with water instead of washing with soap	Serious
Spacer_Critical_50	Does not air dry	Serious
Spacer_Critical_51	Dries with a cloth	Serious

APPENDIX B: Questionnaires

UK 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?	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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

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?	☐	☐	☐	☐	☐	☐	☐	☐

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

About your nose:

	No	Occasionally & little bother	Occasionally & quite a bother	Most days but little bother	Most days & a lot of bother
Do you have any of these symptoms: itchy, runny, blocked nose or sneezing when you don't have a cold?	☐	☐	☐	☐	☐

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 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?	☐	☐	☐

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

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:

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

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*

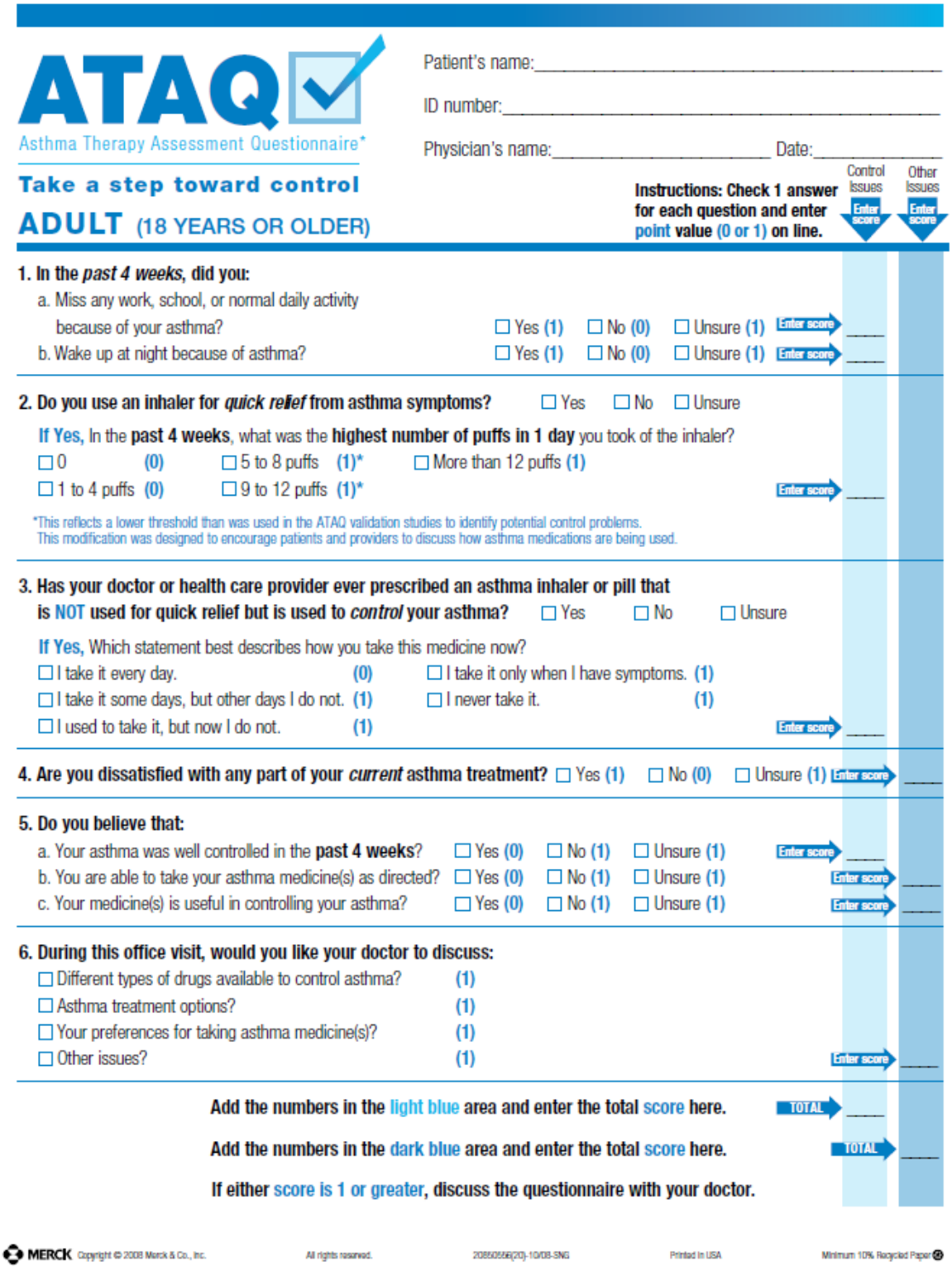
Als u een van deze bovenstaande klachten heeft:

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? _____

Questionnaire to calculate ATAQ scores[b]



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) ☐ 5 to 8 puffs (1)* ☐ More than 12 puffs (1)
   ☐ 1 to 4 puffs (0) ☐ 9 to 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.

[b] Note that question 5 of the ATAQ will score 1 point if the answer is 'no'. The variable ATAQ_Cat is categorised by: a. Well (0 points); b. Not well (1-2 points); c. Poorly controlled (3-4 points)

APPENDIX C: iHARP database

Synopsis of the procedure for generating the iHARP database.

GP practices are invited to participate in the iHARP service. This service offers a thorough review of their moderate to severe (BTS/SIGN step 3 and above) asthma patients and provides feedback to the GPs to assist them in better caring for their patients. Patients registered with the GP surgeries that fit the criteria for iHARP (BTS/SIGN Step 3, prescribed ≥2 prescriptions of FDC ICS/LABA in the prior year, aged ≥18 years old, with co-morbid COPD ruled out and no signs of current unstable disease (see inclusion/exclusion criteria for full details), are then invited, via a postal letter to participate in a review. Those that respond then attend a face-to-face interview with a nurse (or doctor in Spain) who has undergone suitable training to carry out this service.

In the UK, the review consists of a computer-based questionnaire which the nurse completes during the interview, based on information provided by the patient. During this process, the questionnaire will call for spirometry readings (including PIF and PEF) which will be measured at the time of interview and reported. The patient will also be asked to perform an inhalation procedure, using their own device (twice, if their dose is for 2 inhalations), which the nurse can observe for technique errors and record on the questionnaire. Further patient data are also extracted from their medical records (details of the source of data for each variable is detailed in the tables below). For patients also registered on the OPCRD database, recorded data can be cross-checked to confirm its validity.

The procedure for other countries (excluding the Netherlands) is equivalent to the UK service. In the Netherlands, the questionnaire is completed in paper form and some variation in the types of variables recorded exists. These are detailed in the tables below. Australia uses spirometry readings, like the UK, but all other countries use AIMS machines for equivalent measurements. No equivalent to the OPCRD database is available for cross-checking or further data extraction outside of the UK.

The review is a one-time interview focussed on the last 12 months of the patient's asthma (except for co-morbidities that are considered ever). Feedback to GPs and patients following the review hope to better inform them of the level of asthma control currently being achieved and potential ways to make any improvements, particularly with regards to inhaler device technique.

APPENDIX D: Syntax for some variables used in study

Syntax for New_Age_Diagnose:

```
RECODE Year_First_Diagnosed Age_at_Diagnosis (0=SYSMIS) (-1=SYSMIS) (-2=SYSMIS).
EXECUTE.
COMPUTE Age_at_diagnosis_calc=Age - (2012 - Year_First_Diagnosed).
EXECUTE.
RECODE Age_at_Diagnosis (SYSMIS=-1).
EXECUTE.
COMPUTE New_Age_Diagnose = Age_at_Diagnosis.
EXECUTE.
If (Age_at_Diagnosis  = -1)  New_Age_Diagnose=Age_at_diagnosis_calc.
EXECUTE.
VARIABLE LABELS  new_Age_Diagnose 'new age'.
RECODE New_Age_Diagnose  (0=SYSMIS) (-1=SYSMIS) (-2=SYSMIS).
EXECUTE.
RECODE New_Age_Diagnose (0 thru 17=0) (18 thru 30=1) (31 thru 50=2) (51 thru 70=3)
(71 thru
   Highest=4) INTO Age_at_Diagnosis_Cat.
EXECUTE.
```

Syntax for Duration_of_disease:

```
COMPUTE Duration_of_disease=Age - New_Age_Diagnose.
EXECUTE.
RECODE Duration_of_disease (-1=SYSMIS) (Lowest thru -1=SYSMIS).
EXECUTE.
RECODE Duration_of_disease (0 thru 1=0) (2 thru 5=1) (6 thru 10=2) (11 thru 15=3) (16
thru 20=4)
   (21 thru Highest=5) INTO Duration_of_Disease_Cat.
EXECUTE.
```

Syntax for New GINA score:

```
COMPUTE MAX_PEF=MAX(Q_PEF1, Q_PEF2, Q_PEF3, Q_BestPEF).
EXECUTE.

RECODE MAX_PEF (Lowest thru 100=SYSMIS).
EXECUTE.

RECODE Q_FeV1_Reading (-2=SYSMIS) (ELSE=Copy) INTO BEST_FEV1.
EXECUTE.

DO IF  (Gender = 1).
RECODE BEST_FEV1 (ELSE=Copy) INTO BEST_FEV1_Male.
END IF.
EXECUTE.

DO IF  (Gender = 0).
RECODE BEST_FEV1 (ELSE=Copy) INTO BEST_FEV1_Female.
END IF.
EXECUTE.

COMPUTE Pred_FEV1_Male=4.30*(Height) - 0.029*(Age) - 2.49.
EXECUTE.

COMPUTE Pred_FEV1_Female=3.95 * (Height) - 0.025*(Age) - 2.60.
EXECUTE.

COMPUTE Pred_PEF_Male=((5.317 * (Height)) - (0.062 *(Age)) + 3.884) * 60.
EXECUTE.

COMPUTE Pred_PEF_Female=((4.087 * Height) - (0.050 *Age) + 2.945) * 60.
EXECUTE.

DO IF  (Gender = 1).
RECODE MAX_PEF (ELSE=Copy) INTO BEST_PEF_Male.
END IF.
EXECUTE.

DO IF  (Gender = 0).
RECODE MAX_PEF (ELSE=Copy) INTO BEST_PEF_Female.
END IF.
EXECUTE.
```

Syntax for New GINA score (continued):

```
RECODE BEST_FEV1_Male BEST_FEV1_Female (-1=SYSMIS) (0=SYSMIS).
EXECUTE.

COMPUTE Ratio_Best_PEF_Pred_PEF_Male=BEST_PEF_Male / Pred_PEF_Male.
EXECUTE.

COMPUTE Ratio_Best_PEF_Pred_PEF_Female=BEST_PEF_Female / Pred_PEF_Female.
EXECUTE.

COMPUTE Ratio_Best_FEV1_Pred_FEV1_Male=BEST_FEV1_Male / Pred_FEV1_Male.
EXECUTE.

COMPUTE Ratio_Best_FEV1_Pred_FEV1_Female=BEST_FEV1_Female / Pred_FEV1_Female.
EXECUTE.

DO IF (Ratio_Best_PEF_Pred_PEF_Male > 0).
RECODE Ratio_Best_FEV1_Pred_FEV1_Male (ELSE=0).
END IF.
EXECUTE.

RECODE Ratio_Best_FEV1_Pred_FEV1_Male (SYSMIS=0).
EXECUTE.

DO IF (Ratio_Best_PEF_Pred_PEF_Female > 0).
RECODE Ratio_Best_FEV1_Pred_FEV1_Female (ELSE=0).
END IF.
EXECUTE.

RECODE Ratio_Best_FEV1_Pred_FEV1_Female (SYSMIS=0).
EXECUTE.


RECODE Ratio_Best_PEF_Pred_PEF_Male Ratio_Best_PEF_Pred_PEF_Female (SYSMIS=0).
EXECUTE.

COMPUTE Ratio_PEF_AND_FEV1=Ratio_Best_PEF_Pred_PEF_Male +
Ratio_Best_PEF_Pred_PEF_Female +
   Ratio_Best_FEV1_Pred_FEV1_Male + Ratio_Best_FEV1_Pred_FEV1_Female.
EXECUTE.
```

Syntax for New GINA score (continued):

```
RECODE Ratio_PEF_AND_FEV1 (0=SYSMIS).
EXECUTE.

RECODE Ratio_PEF_AND_FEV1 (Lowest thru 0.79=1) (0.8 thru Highest=0) INTO Ratio_PEF_FEV1_Cat.
EXECUTE.

RECODE Q_RCP_Activity Q_RCP_Nights (0=0) (1 thru Highest=1) INTO Q_RCP_Activity_Score
   Q_RCP_Nights_Score.
EXECUTE.

RECODE Q_Reliever Q_RCP_Symptoms (0=0) (1=0) (2=0) (3 thru Highest=1) INTO Q_Reliever_Score
   Q_RCP_Symptoms_Score.
EXECUTE.

COMPUTE GINAscore_New=Q_RCP_Activity_Score + Q_RCP_Nights_Score + Q_Reliever_Score +
   Q_RCP_Symptoms_Score + Ratio_PEF_FEV1_Cat.
EXECUTE.

RECODE GINAscore_New (0=0) (1=1) (2=1) (3 thru Highest=2) INTO GINAscore_New_Cat.
EXECUTE.
```

Finally label:

0 = Controlled
1 = Partly controlled
2 = Uncontrolled

This syntax in SPSS for predicting Q_ATAQ2 from Q_reliever:

```
RECODE Q_Reliever (7=0) (5=1) (6=1) (0 thru 4=0) (8 thru Highest=1) INTO
Q_Reliever_dichotoom.
EXECUTE.
COMPUTE Q_ATAQ2 = Q_ATAQ2.
EXECUTE.
If (Q_ATAQ2  = -2)  Q_ATAQ2=Q_Reliever_dichotoom.
EXECUTE.
```

Appendix E: Mapping q_reliever variable to ATAQ_2 variable

Data:

In the Endpoint Validation Study (E00112) dataset, there are 3131 patients with both q_reliever and ATAQ_2 non-missing.

Definitions:

q_reliever

In the last week, how many times have you used your reliever inhaler? (Options: 0 – 10+).

ATAQ_2

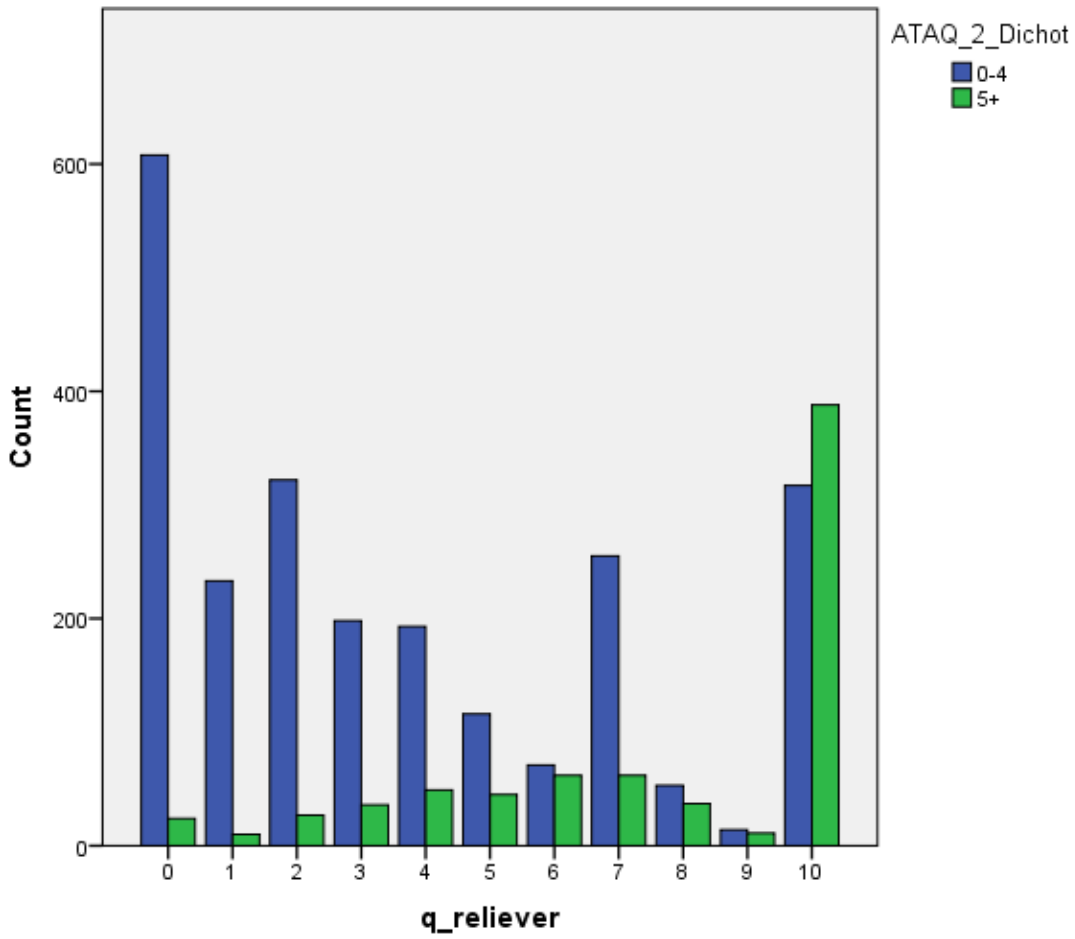
In the past 4 weeks, what was the highest number of puffs in 1 day you took of the reliever inhaler? (Options: 0, 1-4, 5-8, 9-12, 13+).

Problem:

We wish to map the q_reliever value to ATAQ_2 where ATAQ_2 data are missing. ATAQ_2 will be dichotomised 0-4, 5+; and so we need to map the number of times the reliever inhaler was used in the past week to a maximum daily number of puffs of 0-4 / 5+.

Exploratory Data:

q_reliever (# of times used in last week)	ATAQ_2 (Maximum number of puffs per day)		Total
	0-4	5+	
0 n (%)	608 (96.2)	24 (3.8)	632 (100)
1 n (%)	233 (95.9)	10 (4.1)	243 (100)
2 n (%)	322 (92.3)	27 (7.7)	349 (100)
3 n (%)	198 (84.6)	36 (15.4)	234 (100)
4 n (%)	193 (79.8)	49 (20.2)	242 (100)
5 n (%)	116 (72.0)	45 (28.0)	161 (100)
6 n (%)	71 (53.4)	62 (46.6)	133 (100)
7 n (%)	255 (80.4)	62 (19.6)	317 (100)
8 n (%)	53 (58.9)	37 (41.1)	90 (100)
9 n (%)	14 (56.0)	11 (44.0)	25 (100)
10+ n (%)	317 (45.0)	388 (55.0)	705 (100)
Total n (%)	2380 (76.0)	751 (24.0)	3131 (100)



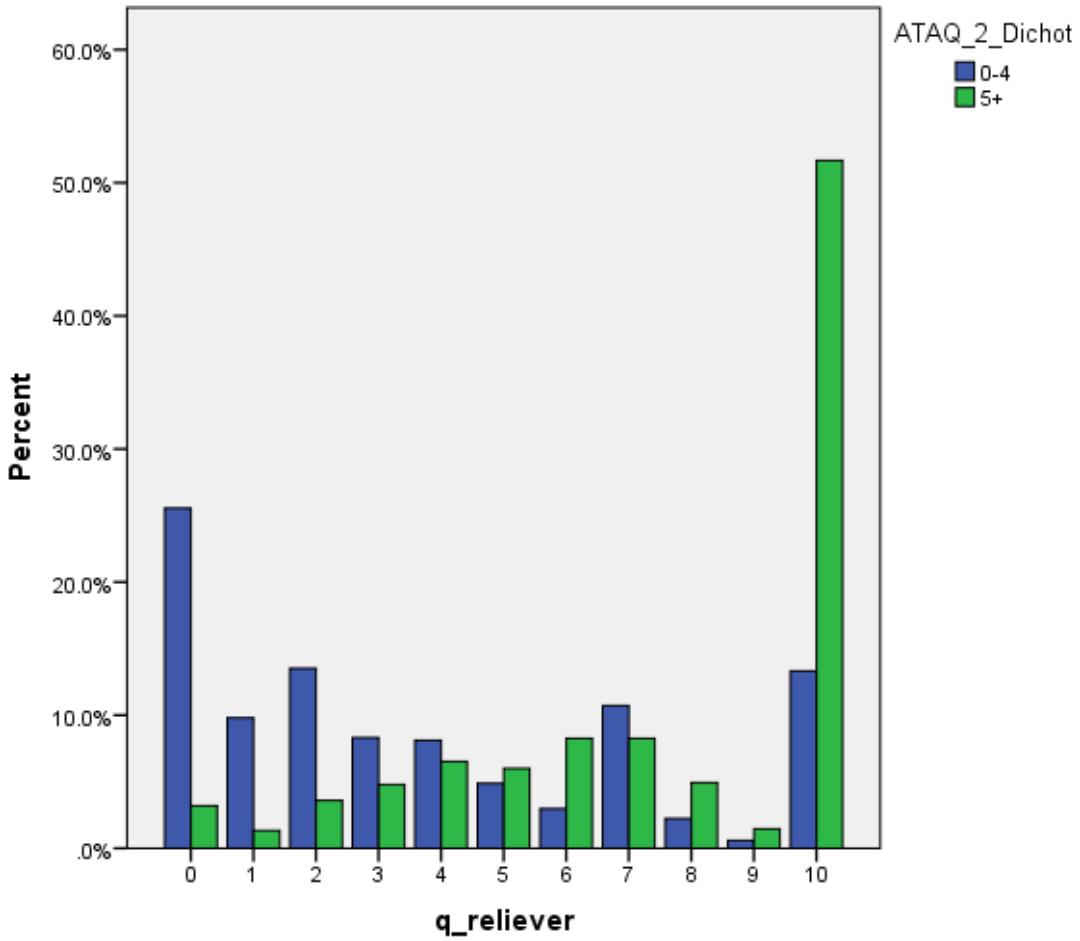
Notes:

76% of patients record 0-4 as maximum number of puffs per day; 24% record 5+.

The percentage of patients recording 0-4 maximum puffs per day decreases with number of times used EXCEPT those who reported approximately daily use (7 times in the last week) report a low maximum number of puffs.

Those using their reliever 10+ times in the last week are more likely to record a high maximum number of puffs (although p = 0.45 / 0.55 for low/high respectively).

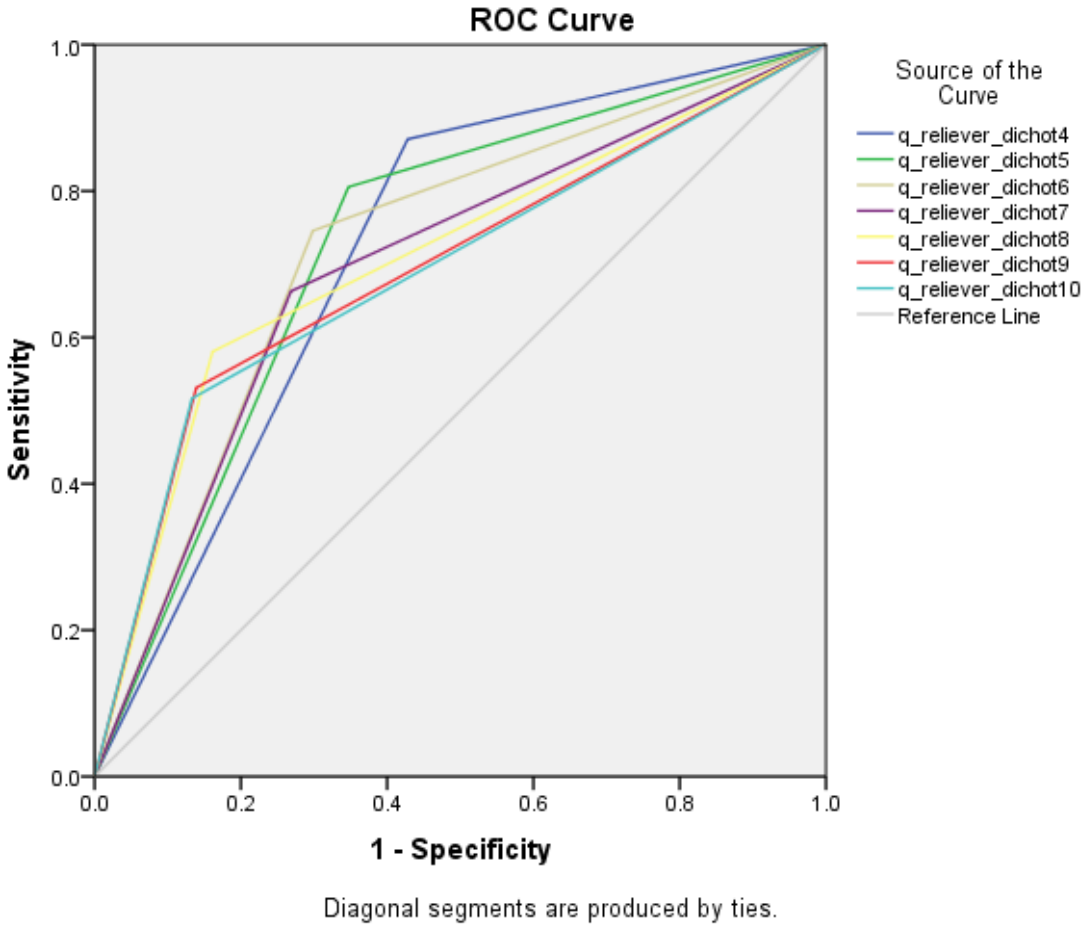
q_reliever (Number of times used in last week)	ATAQ_2 (Maximum number of puffs per day)		Total
	0-4	5+	
0 n (%)	608 (25.5)	24 (3.2)	632 (20.2)
1 n (%)	233 (9.8)	10 (1.3)	243 (7.8)
2 n (%)	322 (13.5)	27 (3.6)	349 (11.1)
3 n (%)	198 (8.3)	36 (4.8)	234 (7.5)
4 n (%)	193 (8.1)	49 (6.5)	242 (7.7)
5 n (%)	116 (4.9)	45 (6.0)	161 (5.1)
6 n (%)	71 (3.0)	62 (8.3)	133 (4.2)
7 n (%)	255 (10.7)	62 (8.3)	317 (10.1)
8 n (%)	53 (2.2)	37 (4.9)	90 (2.9)
9 n (%)	14 (0.6)	11 (1.5)	25 (0.8)
10+ n (%)	317 (13.3)	388 (51.7)	705 (22.5)
Total n (%)	2380 (100)	751 (100)	3131 (100)



Patients reporting a maximum number of puffs per day of < 5 generally report using their reliever inhaler < 5 times in the last week. The anomalies again are: a high proportion (11%) report using it daily; and 13% report using it at least 10 times in the last week.

ROC Curve Analysis:

Treating ATAQ_2 score > 4 as the positive outcome:



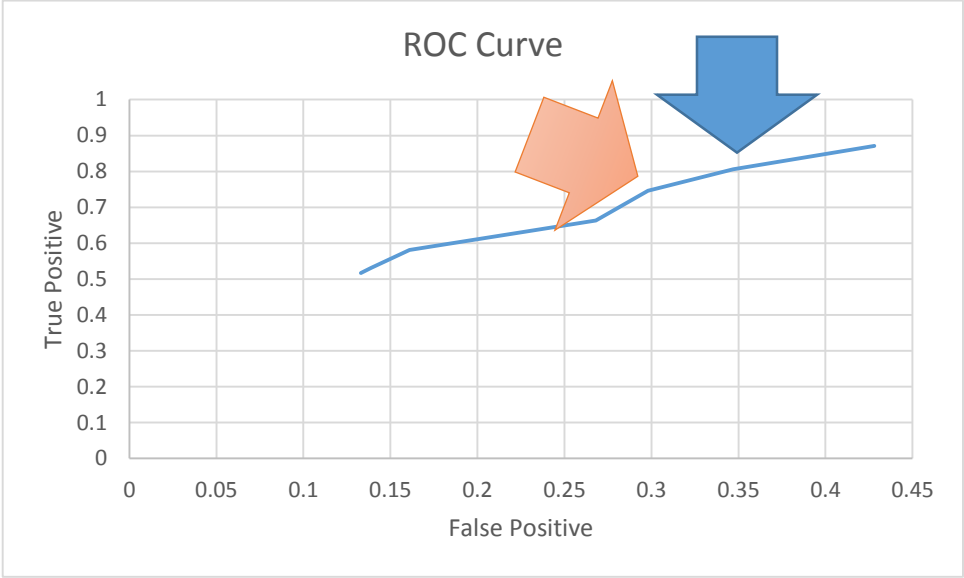
The maximum area under the curve is when the q_reliever score is dichotomised as 0-4 / 5+. (Area similar but slightly lower (i.e. an alternative?) for q_reliever score dichotomised as 0-5 / 6+.

However, in light of the exploratory analysis: if the q_reliever score is dichotomised as 0-4 or 7 / 5-6 or 8+, this gives an even higher area under the curve.

Looking at true positive & false positive rates (where a "true positive" is correctly classifying ATAQ_2 > 4 from a dichotomised q_reliever variable; and a "false positive" is incorrectly classifying ATAQ_2 > 4 from a dichotomised q_reliever variable:

Dichotomisation of the q_reliever variable	True Positive	False Positive
0-4 / 5+	80.6%	34.7%
0-5 / 6+	74.6%	29.8%
0-4 or 7 / 5-6 or 8+	72.3%	24.0%

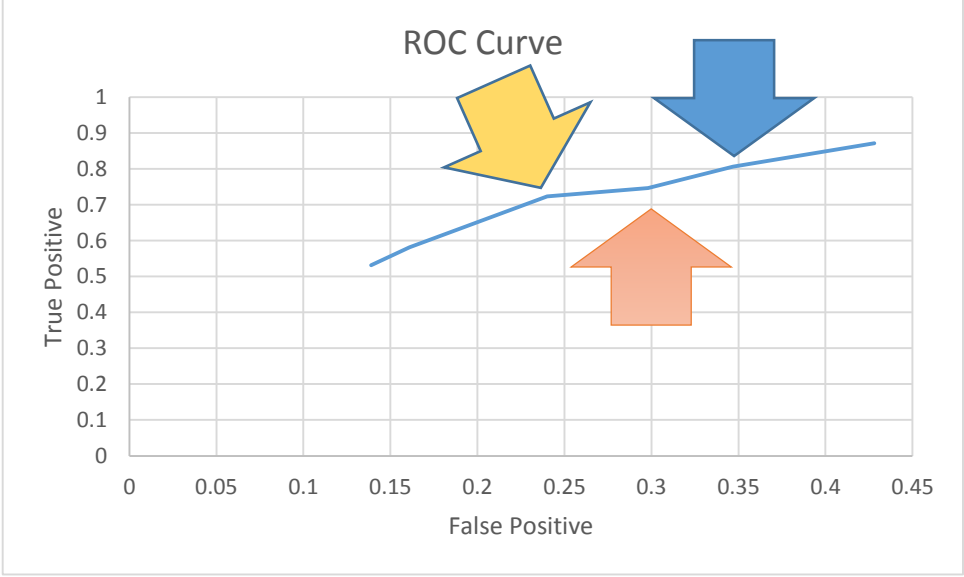
(So a lower true positive for 0-4 or 7 / 5-6 or 8+ but also a lower false positive.)



Key:

0-5 / 6+

0-4 / 5+



0-4 or 7 / 5-6 or 8+

(i.e. between the yellow arrow & the orange arrow there is little gain in true positive for a large increase in false positive.)

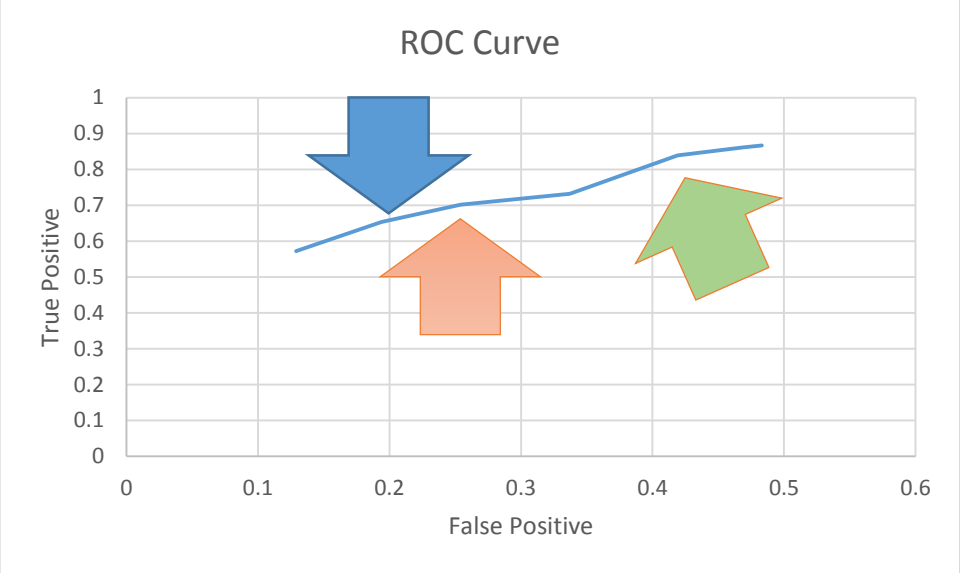
Treating ATAQ_2 score = 0-4 as the positive outcome:

Areas under the curve are as before (maximum area under the curve when the q_reliever score is dichotomised as 0-4 / 5+).

Looking at true positive & false positive rates (where a "true positive" is correctly classifying ATAQ_2 = 0-4 from a dichotomised q_reliever variable; and a "false positive" is incorrectly classifying ATAQ_2 = 0-4 from a dichotomised q_reliever variable:

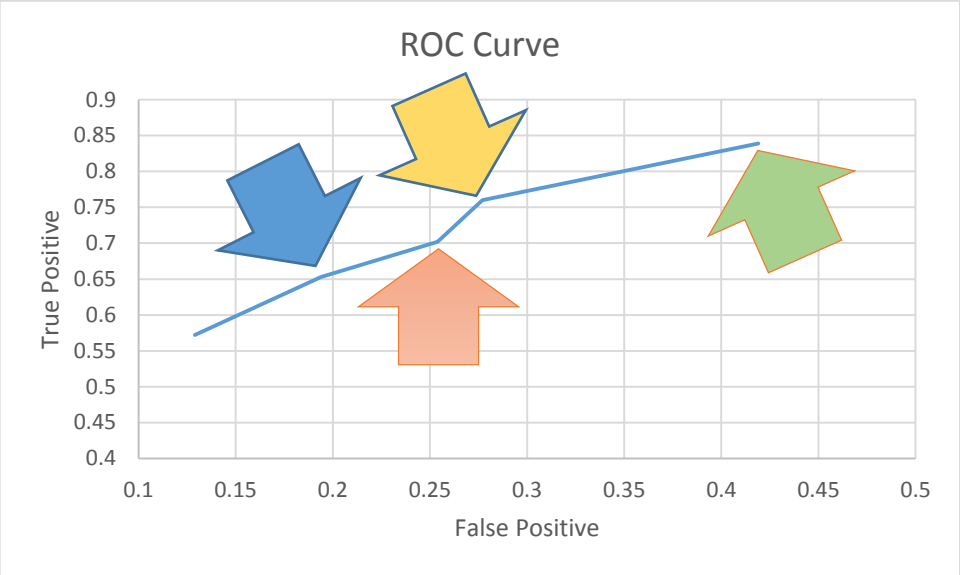
Dichotomisation of the q_reliever variable	True Positive	False Positive
0-4 / 5+	65.3%	19.4%
0-5 / 6+	70.2%	25.4%
0-7 / 8+	83.9%	41.9%
0-4 or 7 / 5-6 or 8+	76.0%	27.7%

(So a good true positive for 0-4 or 7 / 5-6 or 8+ but also a lower false positive.)



Key: 0-5 / 6+ 0-4 / 5+

0-7 / 8+ 0-4 or 7 / 5-6 or 8+



Conclusion:

A simple solution that is good for either ATAQ_2 = 0-4 OR = 5+ as the positive outcome is mapping:

q_reliever = 0-4 onto ATAQ_2 = 0-4

q_reliever = 5+ onto ATAQ_2 = 5+

For ATAQ_2 = 0-4 as the positive outcome, an alternative to give a higher true positive is the mapping:

q_reliever = 0-7 onto ATAQ_2 = 0-4

q_reliever = 8+ onto ATAQ_2 = 5+

However, the best solution is to map:

q_reliever = 0-4 or 7 onto ATAQ_2 = 0-4

q_reliever = 5-6 or 8+ onto ATAQ_2 = 5+