REG STUDY PROTOCOL

LONG TITLE:

COMPARATIVE EFFECTIVENESS OF EXTRA-FINE PARTICLE INHALED CORTICOSTEROID (ICS) AND ALTERNATIVE GUIDELINE-RECOMMENDED STEP-UP OPTIONS IN PRE-SCHOOL CHILDREN

SHORT TITLE: EF ICS IN PRE-SCHOOL CHIDLREN

Research Protocol developed by The Respiratory Effectiveness Group

CONTENTS PAGE

ABBREVIATIONS & DEFINITIONS

Abbreviations

BDP	Beclomethasone dipropionate
EF	Extra-fine
NEF	Fine and standard particle
FDC	Fixed dose combination
FP	Fluticasone propionate
HFA	Hydrofluoroalkane
ICS	Inhaled glucocorticosteroid
LABA	Long-acting bronchodilator
MMAD	Mass Medium Aerodynamic Diameter
RCT	Randomised controlled trial
REG	Respiratory Effectiveness Group
RiRL	Research in Real Life Ltd
SABA	Short-acting bronchodilator

ICS particle size definitions

Extrafine	ICS with particle MMAD <2 microns (e.g. EF HFA BDP [Qvar®] and ciclesonide)
Non-extrafine	Both fine and standard paticle ICS:
Fine	ICS with particle MMAD <5 microns but ≥2 microns (e.g. fluticasone propionate, non-extrafine beclomethasone dipropionate)
Standard particle	ICS with particle MMAD >5 microns

BACKGROUND & RATIONALE

Diagnosing asthma in children

Asthma in children causes recurrent respiratory symptoms of wheezing, cough, difficulty breathing and chest tightness. Wheezing is recognised as one of a number of respiratory noises that occur in children and parents often use the term “wheezing” as a non-specific label to describe any abnormal respiratory noise.[1]

There are many different causes of wheeze in childhood and different clinical patterns of wheezing (or “wheezing phenotypes”) have been recognised through retrospectively evaluations. They cannot reliably be distinguished when an individual child first presents with wheezing. The most common clinical pattern, especially in pre-school children and infants, is episodes of wheezing, cough and difficulty breathing associated with viral upper respiratory infections (colds), with no persisting symptoms. Most of these children will stop having recurrent chest symptoms by school age, but a minority of children who wheeze with viral infections in early life will go on to develop more classical atopic asthma features (developing interval wheezing in response to other triggers.[1]

Differential diagnosis in children

In young children, it can be difficult to differentiate between wheeze and probable asthma. A number of features have been recognised as increasing the probability that a child that presents with respiratory symptoms early in life will go on to develop asthma. Among these features are: [1]

- **Age at presentation:** most children who present with wheeze before the age of 2 years become asymptomatic by mid-childhood.
- **Sex:** male sex is a risk factor for asthma in pre-pubertal children. Female sex is a risk factor for the persistence of asthma in the transition from childhood to adulthood. Boys with asthma are more likely to "grow out" of their asthma during adolescence than girls.
- **Coexistence of atopic disease:** a history of other atopic conditions such as eczema and rhinitis. Positive tests for atopy in a wheezing child also increase the likelihood of asthma as does a raised specific IgE to wheat, egg white, or inhalant allergens such as house dust mite and cat dander and positive skin prick tests and a raised blood eosinophil count.
- **Family history of atopy:** A family history of atopy is the most clearly defined risk factor for atopy and asthma in children. Indeed, the strongest association is with maternal atopy, which is an important risk factor for the childhood
- **Abnormal lung function:** Persistent reductions in baseline airway function and increased airway responsiveness during childhood are associated with having asthma in adult life.

Management of wheeze / asthma in children ≤5 years old

Respiratory guidelines in the UK, suggest that children who have persisting or interval symptoms are most likely to benefit from therapeutic interventions. [1]

The guidelines recommend initaiting children on the treatment step most appropirate to their initial severity of (possible) asthma and that they be moved up, or down, the recommended treatment steps until optimum control is achieved at the lowest therapeutic burden. Concordance with treatment should be checked and the diagnosis reconsidered if treatment response is unexpectedly poor. The treatment steps recommended by the British Thoracic Socity / Scottish Intercollegiate Guideline Network (BTS/SIGN) in the UK for pre-schol children are summarised below. [1]

BTS / SIGN Recommendations for the management of asthma in children under 5yrs

Treatment Step	Step Description	Treatment recommendation
Step 1	Mild intermittent asthma	• SABA as required
Step 2	Regular preventer therapy	• Add ICS (200–400mcg/day*[$]); Start ICS dose appropriate to severity of disease • LTRA if ICS cannot be used
Step 3	Initial add-on therapy	In children: • Taking: ICS 200–400mcg/daily, consider addition of LTRA • Taking: LTRA alone, reconsider addition of ICS 200-400mcg/daily • <2 years, consider proceeding to step 4
Step 4	Persistent poor control	Refer to respiratory paediatrician

*BDP equivalent; [$]High nominal doses may be required if drug delivery is difficult

Small Airways Inflammation

The Montreal Protocol mandated discontinuation of chlorofluorocarbons (CFCs) use in medical inhalers.[2] In their place alterantive, some new inhaled corticosteroid (ICS) formulations were developed, such as beclometasone dipropionate (BDP) extrafine aerosol, which used hydrofluoroalkane (HFA), rather than CFCs, as the propellant. Unlike traditional CFC-based inhalers, the ICS particles in BDP extrafine aerosol are held in a solution, rather than a suspension of propellant. In addition, the average particle size of BDP extrafine aerosol is smaller, the velocity of the particles leaving the inhaler on actuation is slower, the duration of the spray is longer and the temperature of the spray is warmer compared with that of traditional inhalers.[3] As a result, a softer more gentle spray is produced, fewer BDP particles impact on the oropharynx and more drug reaches the lung, particularly the small airways.[3-5]

In studies of both adults and children with asthma, BDP extra-fine (EF) aerosol produced equivalent asthma control at approximately half the daily dose compared with CFC-based BDP inhalers and the budesonide pressurized metered-dose inhaler (MDIs).[6–12] The approximate 2:1 dosing ratio of BDP EF aerosol to CFC-BDP is attributed to the greater fine particle fraction and increased lung deposition of BDP. When compared with a more potent ICS in adults with mild-to-moderate asthma, BDP extrafine aerosol provided equivalent asthma control to CFC-based fluticasone propionate (FP) at approximately the same dose.[13,14]

Furthermore, a number of observational studies (using routine clinical practice data) including those conducted by the Respiratory Effectiveness Group's (REG) Small Airways Study Group (SASG) suggest that EF ICS offers at least equivalent outcomes (at appreciably lower dose) than non-EF (NEF) ICS alternatives. These findings have been consistent across the SASG's portfolio of studies, both US (claims) and UK (primary care electronic medical record) asthma studies, in COPD studies and in selected patient subgroups (e.g. asthmatic smokers).[15-19]

Small airways and management of pre-school asthma/wheeze

The particle size (and delivery characteristics of EF HFA BDP) aerosol may be particularly relevant for young children in whom a greater proportion of airways are classified as small (i.e. <2mm in diameter)[4] and airways resistance is low.

At the time of writing, there are evidence to suggestion that EF HFA BDP is equivalent to CFC-FP in terms of efficacy and safety in adults and children (5–12 years) with mild-to-moderate asthma.[14,20] However, evidence remains lacking as to the role that ICS particle size may play in the management of asthma/wheeze in younger, pre-school (<5 years) children.

AIM & OBJECTIVE

The aim of this study is to test the hypothesis that use of EF ICS in pre-school children (i.e. ≤5 years of age) with asthma/wheeze will achieve better outcomes than treatment alternatives (i.e. NEF ICS, LTRA, or SABA) .

STUDY DESIGN & DATASET

Data source

The Optimum Patient Care Research Database (**OPCRD)** comprises data extracted through the Optimum Patient Care (OPC) Clinical Service Evaluation. The clinical evaluation involves a combined review of (anonymised) electronic medical records (EMRs) and patients' responses to disease-specific questionnaires and characterizes patients in terms of their demography, disease control and exacerbation history. The review process produces patient-level reports that offer guideline-based recommendations for possible management changes to optimise control at the lowest possible therapeutic dose and reduce potential future exacerbation risk.

At the time of writing, OPCRD contains anonymised, research-quality data for over 2.5 million patients with asthma collected from more than 525 practices across the UK that subscribe to the OPC Clinical Service Evaluation (see **Appendix 1** for OPCRD Data Dictionary). The OPCRD will be extending its service to capture asthma-specific questionnaire data and patient reported outcomes for children, but questionnaire data are not currently available for the preschool population proposed in this study design.

Study Design

This will be a prospectively planned (and registered) matched cohort study drawing on retrospective, EMRs from the OPCRD. It will consist of two main phases:

Phase I: a descriptive analysis of treatment patterns in children aged ≤5 years with wheezing illness to help characterise the clinical features of wheezing illness and to improve understanding of how therapeutic options are routinely prescribed. Phase I will serve as a feasibility assessment for Phase II, i.e. to establish that there are sufficient EF ICS patients within the study population to support the proposed design of the Phase II analysis.

Part II:
Primary analysis: a comparative effectiveness evaluation of guideline-recommended treatment options in pre-school children newly initating Step 2 therapy NEF ICS vs EF ICS and LTRA vs EF ICS over a 1-year outcome period.

EF ICS will be the reference treatment to evaluate whether EF ICS formulations offer benefit over alternative treatment options in early-life wheezing illness/

Exploratory analysis: an extension of the primary analysis over a 5-year outcome period to explore whether EF ICS may offer potential disease-modifying effects compared with alternative treatment options when used in the management of early-life wheezing illness.

Exposures

Exposures of interest will include:

- Active:
  - EF ICS (EF HFA BDP or ciclesonide) via pMDI
  - NEF ICS (NEF BDP or FP) via pMDI
  - LTRA
- Control: SABA

Study Period

The date of last extraction from the OPCRD will be 31 December 2014.

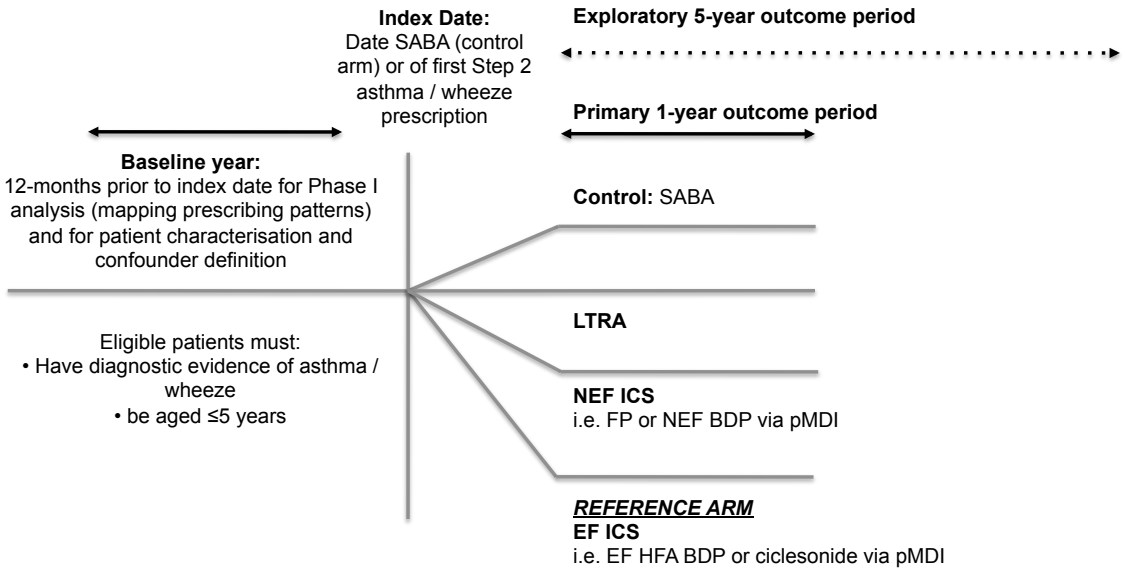
The study will consist of a baseline year immediately prior to, and an outcome period immediately following the index date.

The index date will be the date at which patients receive their first prescription for active therapy (EF ICS via pMDI, NEF ICS via pMD, LTRA) or (in matched controls) a repeat SABA prescription.

The study period will run for a continuous:

- **Primary analysis**: ≥2-year period (at least one baseline year before the index date and one outcome year after the index date)
- **Exploratory analysis:** ≥6-year period (at least one year baseline period before the index date and six year outcome peirod after the index date).

Study design schematic



STUDY POPULATION

Eligibility Criteria

Inclusion criteria

To be eligible for inclusion in the study, patients must meet the following criteria:

- **Age:** ≤5 years of age at the index date
- **Evidence of pre-school wheeze or asthma during the baseline year –** defined as either:
  - ≥2 wheezing episodes recorded within their primary care records in the baseline year, or
  - ≥2 prescriptions (at two different points in time) during the baseline year for any combination of oral steroids coded for a lower respiratory complaint ± salbutamol

- **Active treatment during outcome year:**
  - Active treatment arms (Step 2 therapy): ≥2 prescriptions (i.e. ≥1 in addition to that prescribed at index date) for any of the Step 2 treatment options (i.e. any ICS via pMDI or LTRA).
  - Control arm: ≥2 prescriptions for SABA.
  - Exploratory 5-year outcome analysis: ≥1 prescription of the index date therapy in each of the outcome years
- **At least 2 year's continuous records:** ≥1 year's continuous baseline records and ≥1 year's outcome records.
  - Eligibility for the exploratory analysis ≥5-years'outcome data.

Exclusion criteria

Patients will be excluded if they:

- Have a physician diagnosis for any chronic respiratory disease, except wheeze or asthma.
- Received a combination inhaler in addition to a separate ICS inhaler in baseline;
- Multiple step-up therapies on the same day
- Infants: any child under the age of 1 year (as ≥1 year of baseline data is required).

OUTCOMES

The endpoints used in this study will mirror/repeat those used in previous, published comparative effectiveness studies conducted by the Respiratory Effectiveness Group using the OPCRD.[16-19]

Primary endpoint

1a) Exacerbations (ATS/ERS definition) defined as occurrence of an:

- Asthma-related: Hospital admissions OR A&E attendance; OR
- An acute course of oral steroids (coded for asthma or wheeze).

1b) Exacerbation (ATS/ERS definition sensitivity) defined as occurrence of:

- Asthma-related: Hospital admissions OR A&E attendance; OR
- An acute course of oral steroids with lower respiratory consultation

Where "asthma-related" indicates an accompanying asthma-code; "evidence of respiratory review" indicates an accompanying lower respiratory code.

Secondary endpoints

2.1a) Acute respiratory event: defined as occurrence of:

- Asthma-related: hospital admissions OR A&E attendance; OR
- An acute course of oral steroids (coded for asthma); OR
- Antibiotics prescribed with lower respiratory consultation

2.1b) Acute respiratory event (sensitivity) defined as occurrence of:

- Asthma-related: hospital admissions OR A&E attendance; OR
- An acute course of oral steroids with lower respiratory consultation; OR

- Antibiotics prescribed with lower respiratory consultation.

2.2a) Risk Domain Asthma Control defined as absence of:

Controlled:
- Asthma-related: Hospital admission AND A&E attendance, AND Out-patient department attendance; AND
- Acute use of oral steroids; AND
- Antibiotics prescribed with lower respiratory consultation.

Uncontrolled: all others.

2.2b) Risk Domain Asthma Control (sensitivity) defined as absence of:

Controlled:
- Asthma-related: Hospital admission AND A&E attendance, AND Out-patient department attendance; AND
- Acute use of oral steroids with lower respiratory consultation; AND
- Antibiotics prescribed with lower respiratory consultation.

Uncontrolled: all others.

2.3) Overall Asthma Control (OAC): risk and impairment defined as:
- Risk Domain Asthma Control (achievement / non-achievement); plus
- Average daily dose of UK ≤200mcg salbutamol (or equivalent)

2.4a) Treatment stability: Excluding changes in therapeutic regimen that are likely to be motivated by cost-savings.

Stable:
- Achieved Risk Domain Asthma Control (as defined above); AND
- No additional therapy defined as no:
  - Increased dose of ICS (≥50% increase of that prescribed at index date) AND/OR
  - Use of additional therapy as defined by: long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs).

Unstable: all others.

2.4b) Treatment stability (sensitivity): Excluding changes in therapeutic regimen that are likely to be motivated by cost-savings.

Stable:
- Achieved Risk Domain Asthma Control (as defined above); AND
- No additional therapy defined as no:
  - Increased dose of ICS (≥50% increase of that prescribed at index date) AND/OR
  - Change in ICS AND/OR
  - Change in delivery device AND/OR
  - Use of additional therapy as defined by: long-acting bronchodilator (LABA), theophylline, leukotriene receptor antagonists (LTRAs).

Unstable: all others.

2.5) SABA usage

Average daily SABA dosage during outcome year, calculated as average number of puffs per day over the year multiplied by strength (in mcg);

i.e. $$\frac{Number\ of\ inhalers * doses\ per\ inhaler}{365} * strength$$

and categorised as appropriate to the data.

2.6) Controller-to-Reliever Ratio

$$\frac{\text{Number of controller units}}{\text{Number of controller units} + \text{Number of reliever units}}$$

Controllers: ICS and LTRA. For ICS a unit is taken to be one inhaler; for LTRA a unit is one prescription.

Relievers: SABA, with a unit taken to be one inhaler.

Note:

- LABA is not included as a controller (as the number of "controllers" maybe distorted by fixed combination /separate inhalers).
- Please note that when inhaler duration is very different and not comparable between two treatment groups, the number of controller units – and so Controller to Reliever Ratio - is a biased outcome and results are not meaningful.

The ratio is usually categorised as a dichotomous variable: <0.5 (low) and ≥0.5 (high). A higher Controller-to-Reliever ratio (≥0.5) has been proven to be significantly related to improved asthma-related quality of life, better disease control and reduced symptoms.

2.7a) Oral thrush

Topical anti-fungal prescriptions **definitely** for oral thrush AND/OR oral candidiasis.

2.7b) Oral thrush (senstitivity)

Topical anti-fungal prescriptions ± code for oral thrush AND/OR oral candidiasis

Exploratory endpoints

1. Medication Posession Ratio (proxy for adherence)

$$\frac{\text{Number of days supply of drug}}{365} \; x \; 100$$

MPR is usually categorised as a dichotomous variable: <80% (non-adherent) and ≥80% (adherent).

2a) Confirmed Pneumonia: Read coded + X-ray

2b) Pneumonia: Read coded

3) **Growth Record:** An additional exploratory endpoint will seek to capture clincially relevant information contained within the patients' growth records (with a possible view to linking it to ICS dose in relevant patients). The definition of this endpoing will be confirmed following a review of the growth records once the study population's records has been extracted.

ANALYSIS; VARIABLES & STATISTICAL APPROACH

Analysis

Phase I

A descriptive analysis of treatment patterns in children aged ≤5 years with wheezing illness to improve understanding of the clincial features of the condition and also how therapeutic options are routinely prescribed.

The study population and a control population will be characterised over the one-year baseline period in terms of demography, clinical characteristics and healthcare resource utlisation.

In addition, prescribing patterns in the primary (1-year) outcome period will be mapped—non-grouped data—to improve understanding of prescribing habits and to inform the outcomes for Phase II.

The following will be described over the primary outcome period:

- Asthma prescriptions prescribed
  - Number of prescriptions
  - Duration of prescriptions
  - Medication posession ratio
  - Mean daily dose (for the active, ICS arms)
  - ICS inhaler device prescribed
- Number of antibiotic courses prescribed

Phase II

2-way matched comparisions

Propsectively designed, retrospective three, two-way matched comparative effectiveness analyses of: EF ICS compared with LTRA therapy, and of NEF ICS compared with LTRA therapy over a 1-year (primary) and 5-year (secondary) outcome period.

Patients in the SABA treatment arms will be matched (in terms of key baseline clincial and demographic characteristics) to patients in the LTRA, EF ICS and NEF ICS treatment arms to minimise the risk of potential confounding by indication.

Comparision vs EF ICS

In order to test the hypothesis that ICS therapies with an EF particle fraction may afford greater benefit in this pre-school asthma/wheeze population, the releative benefit of EF ICS vs SABA will be compared to that of the alternative step-up options.

Variables

VARIABLE	POINT / PERIOD OF EVALUATION			
	During baseline	**At index date**	**During the primary outcome year** (and over exploratory outcome years)	**Ever**
Demographics				
Age	X			
Sex	X			
Weight	X		X	
Height	X		X	
BMI[1]	X		X	
Parental smoking (maternal)	X			
6-week check-up data: length	X			
6-week check-up data: length	X			
Growth Records	X		X	
Clinical features				
General				
Primary care consultations	X	X	X	
Hospitalisations	X	X	X	
A&E attendances	X	X	X	
Asthma-specific measures (where available)				
Asthma diagnosis				X
SABA device type	X	X	X	
SABA prescriptions (number); inhaler number	X	X	X	
Asthma consultations	X	X	X	
Asthma out patient department attendances	X	X	X	
LABA use	X	X	X	
Add-on asthma therapies	X	X	X	
ICS device type (metered-dose inhaler [MDI], breath-actuated inhaler [BAI] or dry powder inhaler [DPI])		X	X	
Exposure medication posession ratio[2]		X	X	
Spacer use with an ICS MDI during		X	X	
ICS prescriptions		X	X	
ICS inhalers prescribed		X	X	
ICS duration (total pack days)		X	X	
ICS prescription days (actual period)		X	X	
ICS prescribed dose (most recent)		X	X	
ICS average daily dose (µg in beclometasone equivalents per day)		X	X	
SABA prescriptions	X	X	X	
SABA inhalers prescribed	X	X	X	
Average SABA dosage (average	X	X	X	

µg taken per day)[3]				
Leukotriene receptor antagonist (LTRA) average daily dose (µg/day)		X	X	
Asthma Predictive Index (positive before the age of 3 years)	X			
Acute respiratory events				
Asthma-related[4] hospitalisations (inpatient admissions)	X	X	X	
Asthma-related or A&E (i.e. ER) attendance	X	X	X	
An acute course of oral corticosteroids[5]	X	X	X	
Antibiotic prescriptions with lower respiratory[6] consultation	X	X	X	
Comorbid diagnoses or treatment				
Eczema diagnosis + topical steroid				X
Rhinitis diagnosis and/or prescriptions for nasal steroids				X
Anaphylaxis diagnosis				X
Diabetes diagnosis	X		X	
GERD diagnosis and/or prescriptions for treating GERD	X			
Paracetamol prescribed (yes/no)	X	X	X	
NSAIDs prescribed (yes/no)	X	X	X	
Blood eosinophil count[7]	X	X	X	
Antifungals (±code for oral candidiasis or oral thrush)	X		X	

Variable definitions

1: BMI: defined as the ratio of weight (kg) to squared height (m^2) recorded closest to the end of each study year, and categorised as 'underweight'; 'normal weight'; 'overweight' and 'obese'

2: Calculated as follows for the whole baseline period: (total pack days / baseline period in days) x 100; total pack days = sum of number days per pack; number days per pack = number of actuations per pack / number of actuations per day.

3: 500 µg of terbutaline are considered equivalent to 200 µg of the other SABAs.

4: A definite asthma emergency attendance or asthma hospital admission; or a generic hospitalisation Read code which has been recorded on the same day as a lower respiratory consultation

5: Defined as: (a) all courses that are definitely not maintenance therapy; and/or (b) all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed); and/or (c) all courses with no dosing instructions, but unlikely to be maintenance therapy due to prescription strength or frequency of prescriptions. Maintenance therapy is defined as prescriptions with daily dosing instructions of ≤10mg prednisolone or prescriptions for 1mg or 2.5mg prednisolone tablets where daily dosing instructions are not available.

6: Refers to any 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; or (d) any additional respiratory examinations, referrals, chest x-rays or events.

7: counts ($x10^9$/L), at any time before or within each study year and categorised as high/normal thresholds to be informed by the study steering committee

Statistical approach

Descriptive analysis

Summary statistics will be presented as appropriate for each variable:

- Variables measured on the interval or ratio scale: n and % of non-missing data; mean (standard deviation) and median (inter-quartile range)
- Categorical variables: n (%) of non-missing data; n (%) per category

Treatment cohorts were compared at baseline using the Mann–Whitney test for continuous variables and the Chi-squared test for categorical variables.

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p<0.10$.

Matched analysis

Patients will need to be matched on key demographic and asthma-related characteristics during the baseline year to ensure similarity of patients. Matching criteria will be decided following a thorough review of the baseline data to ensure identification of the most appropriate matching variables. These are likely to include:

- Age
- Sex
- Index prescription date
- Asthma consultations not resulting in an oral steroid prescription
- Baseline SABA usage
- Potential atopic component (yes/no)
- Spacer use (yes/no)
- Average daily ICS dose (within categories computed based on baseline usage)

Conditional logistic regression will be used to compare baseline characteristics between matched cohorts. Any variables that remained potentially different between matched cohorts at baseline ($p<0.10$) will be included as potential confounding factors in the outcome analysis.

Conditional logistic regression will be used to compare cohorts for binary outcomes; and a conditional Poisson regression model will be used to compare outcome exacerbation rates.

Those variables that are potentially different between treatment cohorts at baseline (assuming that they were not collinear with each other, in which case the one most likely to be clinically meaningful will be used) or that are predictive of outcome in a multivariate analysis will be included as potential confounding factors.

The robustness of the outcomes will also be tested for consistency across a number of subgroup and sensitivity / exploratory analyses (see below).

Interaction analysis

Interaction analysis will be used to explore differential treatment outcomes for clincial characteristics known to be associated with a greater probability of childhood asthma (rather than wheeze). Variables of particular interest are noted below – a full analysis approach will be outlined in the study's statistical analysis plan (once developed).

1. **Atopic history:**
   - Evidence of personal atopy
   - No evidence of personal atopy, but evidence of maternal atopy*
   - No evidence of personal or maternal atopy

   Where evidence of atopy will be defined as:

   - **Evidence of eczema:** ≥2 prescriptions for topical steroids coded for eczema, AND/OR
   - **Evidence of allergic rhinitis:** A diagnosis of allergic rhinitis (receipt at >12 months of age) plus ≥2 prescriptions for anti-histamine or nasal steroids

   AND
   Where evidence of ***maternal atopy*** will be defined as:
   - **Asthma diagnosis;** AND/OR
   - **Allergic rhinitis;** AND/OR
   - **Eczema diagnosis** after the age of 16 years

   Maternal records will be linked to children's records using the following algorithm – mother and child if:
   - Available post-code data is consistent for both individuals
   - Delivery date (mother) precedes the 6-weekly check up (child) by ≤8 week
2. **Gender**
3. **Index date coding:**
   - Asthma
   - Wheeze
4. **Maternal smoking**
5. **Age:**
   - 1–3 years (at index date)
   - 4–5 years (at index date)
6. **Disease severity:**
   - <3 episodes of wheeze during baseline
   - ≥3 episodes of wheeze during baseline
7. **Components of the Asthma Predictive Index (API)[21] before the age of 3:** defined as ≥1 major criteria OR ≥2 minor criteria as detailed below.

	API criterion	**Study Proxy**
Major API Critieria	Parent with asthma	Maternal asthma identified as described above
	Physician diagnosis of atopic dermatitis (often called eczema)	As per evidence of atopy as defined above
	Evidence of sensitization to allergens in the air	No proxy available / data will not be recorded
Minor API Criteria	Evidence of food allergies	No proxy available / data will not be recorded
	4 percent or more blood eosinophilia	Blood eosinophil count (where recorded)
	Wheezing apart from colds	Wheeze read codes in the absence of concurrent code codes

8. A study-generated composite of factors associated with persistent wheeze at age 6 years[1]

[1] This will be included subject to associated resource implications and feasibility, but would provide an alternative to the API based on routinely collected patient data

Exploratory analyses

5-year outcome period

As a 5-year outcome period may affect the number of patients (and related power) of the study, this longer outcome period is proposed as an exploratory outcome only. To be eligible for inclusion, patients must have been exposed (defined as ≥1 prescription for their index date therapy) in each of the outcome years.

This analysis will consider only the sub-population of patients aged 1–3 years at index date.

This exploratory analysis builds on elements of the Prevention of Early Asthma in Kids (PEAK) study.[22] It is aims to evaluate the hypothesis that treatment with extra-fine particle (EF) ICS may result in better long-term outcomes than treatment with non-EF (NEF) particle ICS in young children with asthma and that treating young children with asthma with EF ICS may result in a lower rate of progression of asthma therapy (i.e. either an increase in dose of ICS or addition of other controllers such as montelukast, LABA, omalizumab) over 5 years than treatment with non-EF ICS. Any differs between EF ICS and comparator treatment arms in terms of diabetes diagnosis; growth records and lung function (where evaluable) will also be of interest.

STEERING COMMITTEE & STUDY TEAM

The study will be overseen by an independent steering committee comprising members of REG's Small Airways Study Group (SASG) and the Child Health Working Group.

REG is a not-for-profit research and advocacy organization that brings together respiratory experts from around the world with the shared goal of raising the quality and profile of real-life research (both observational studies and pragmatic trials) through a series of research, communication, standards-related and advocacy activities.

The analysis will be conducted by Research in Real Life Ltd (RiRL) on behalf of the REG Lead Invesgitator & Steering Committee. RiRL are a Cambridge-based (UK) expert real-life research organisation with practical experience of conducting real-life observational studies and interpreting real-life study (pragmatic trial and observational) data for ten years.

This protocol has been informed by the views and suggestions of the Lead Investigator and REG Chairman; the data from the study, subsequent analyses and its dissemintation will be approved by the steering committee. The composition of the study steering group is detailed below.

Steering Committee Members

Lead investigator

Jonathan Grigg: Blizard Institute, Queen Mary, University of London, London, UK

Members of the REG Small Airways Study Group & Child Health Working Group

Steering Committee Member	Member of SASG	Member of Child Health Working Group
Wim van Aalderen Emma Children's Hospital AMC, Amsterdam, The Netherlands	✓	✓
Wanda Phipatanakul, Boston Children's Hospital, Boston, MA, USA	✓	✓
Richard Martin Department of Medicine, National Jewish Health, Denver, CO, USA	✓	
Alberto Papi S.Anna University Hospital, Ferrara, Italy	✓	
Nicolas Roche University of Paris Descartes, Paris, France	✓	
David Price Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK	✓	
Theresa Gulibert Children's Hospital Medical Center, Cincinnati, USA		✓
Stan Szefler Children's Hospital Colorado, Denver, Co, USA		✓
Steve Turner Clinical Lecturer, University of Aberdeen, UK		✓
Alan Kaplan Primary Care Physician, Toronto, Canada		✓
James Paton Clinical Reader (Child Health), University of Glasgow		✓
Teoh Oon Hoe KK Women's and Children's Hospital, Singapore		✓
Clare Murray University of Manchester and Royal Manchester Children's Hospital, Manchester, UK		✓

Research

Data analysis and statistical support will be contracted from Research in Real Life Limited.

Proposal Development & Project Management Oversight

Alison Chisholm: REG Chief Scientific Officer

Patient involvement

At the time of writing, there are no patient experts or advocates involved in the planning and/or review of this study.

ETHICS

The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use, and this study protocol will be submitted to OPCRD's Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval to sanction the use of the OPCRD for the purposes of the proposed study.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies a number of limitations existed such as incomplete data and the need to use proxy measures where explicit data are not available. The proposed subset analyses and sensitivity analyses will aim to test the robustness of the data in more tightly defined subgroups, and also its generalisability to a broader, more heterogeneous routine care population.

The proposed matching approach will also aim to minimise counfounding by severity, such that outcomes in like-patients (in terms of both clincial and demograhic characteristics) are compared over the outcome period.

The data from observational studies should be viewed as one element of the overall evidence base and considered in combination with data from other study designs, e.g. pragmatic trials and randomized controlled trials (RCTs).

DATA DISSEMINATION PLANS

REG is committed to registering all research that it conducts (on the ENCePP e-registry) and to publishing all study findings in order to ensure: (i) transparency of its activities and (ii) so that REG-funded research can be used to inform the research and lay community.

At least one abstract from the study will be submitted to a key international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar) and at least one manuscript will be developed and submitted for to a peer review respiratory journal to disseminate the primary elements of the planned analysis.

REFERENCES

1. British Thoracic Society/Scottish Intercollegiate Guideline Network 101. British Guideline on the Management of Asthma: A national clinical guideline May 2008; Revised January 2012. Available online at: https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-guideline-on-the-management-of-asthma/
2. The Montreal Protocol. The Montreal Protocol on substances that deplete the ozone layer. Final Act (Nairobi: UNEP 1987). Federal Reg. 1994;59:56276–56298.
3. Leach, C.L. Effects of formulation parameters on hydrofluoroalkane-beclomethasone dipropionate drug deposition in humans. J Allergy Clin Immunol. 1999;104:S250–S252.
4. Leach, C.L., Davidson, P.J., Boudreau, R.J. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. Eur Respir J. 1998;12:1346–1353.
5. Aalderen WMC, Price D, De Baets FM, Price J. Beclometasone dipropionate extrafine aerosol versus fluticasone propionate in children with asthma. Respiratory Medicine. 2007;101:1585–1593
6. Van Schayck, C.P., Donnell, D. The efficacy and safety of QVAR (hydrofluoroalkane-belcometasone dipropionate extrafine aerosol) in asthma (Part 2): clinical experience in children. Int J Clin Pract. 2004;58:786–794.
7. Davies, R.J., Stampone, P., O'Connor, B.J. Hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol provides equivalent asthma control to cholorfluorocarbon beclomethasone dipropionate at approximately half the total daily dose. Respir Med. 1998;92:23–31.
8. Gross, G., Thompson, P.J., Chervinsky, P., Vanden Burgt, J., and the study group. Hydrofluoroalkane-134a beclomethasone dipropionate, 400µg, is as effective as chlorofluorocarbon beclomethasone dipropionate, 800µg, for the treatment of moderate asthma. Chest. 1999;115:343–351.
9. Fireman, P., Prenner, B.M., Vincken, W., Demedts, M., Mol, S.J., Cohen, R.M. Long-term safety and efficacy of a chlorofluorocarbon-free beclomethasone dipropionate extrafine aerosol. Ann Allergy Asthma Immunol. 2001;86:557–565.
10. Reichel, W., Dahl, R., Ringdal, N., Zetterstrom, O., van den Elshout, F.J., Laitinen, L.A. Extrafine beclomethasone dipropionate breathe-actuated inhaler (400mcg/day) versus budesonide dry powder inhaler (800mcg/day) in asthma. Int J Clin Pract. 2001;55:100–106.
11. Szefler, S.J., Warner, J., Staab, D. et al, Switching from conventional to extrafine aerosol beclomethasone dipropionate therapy in children: a 6-month, open label, randomized trial. J Allergy Clin Immunol. 2002;110:45–50.
12. Worth, H., Muir, J., Pieters, W. Comparison of hydrofluoroalkane beclomethasone dipropionate Autohaler with budesonide Turbuhaler in asthma control. Respiration. 2001;68:517–526.
13. Scheinmann P, Staab D, de Boeck C, et al. A double-blind comparison of budesonide (B) and beclomethasone extrafine aerosol (Q) in children with symptomatic asthma. Allergy 2003; 58 (suppl 135): 74 (abstract 445).
14. Aubier, M., Wettenger, R., Gans, S.J. Efficacy of HFA-beclomethasone dipropionate extra-fine aerosol (800µg/day) versus HFA-fluticasone propionate (1000µg/day) in patients with asthma. Respir Med. 2001;95:212–220.
15. Barnes N, Price D,Colice G, et al. Asthma control with extrafine-particle hydrofluoroalkane–beclometasone vs. large-particle chlorofluorocarbon–beclometasone: a real-world observational study. Clin Exp Allergy. 2011;41; 1521–1532.
16. Price D, Martin RJ, Barnes N, et al. Prescribing practices and asthma control with HFA-BDP and FP: a real-world observational study. JACI 2010;126(3):511-518 e511-510.

17. Martin RJ, Price D, Roche N, et al. Cost-effectiveness of initiating extrafine- or standard size-particle inhaled corticosteroid for asthma in two health-care systems: a retrospective matched cohort study. NPJ Prim Care Respir Med. 2014;24:14081.
18. Postma DS, Roche N, Colice G, et al. Comparing the effectiveness of small-particle versus large-particle inhaled corticosteroid in COPD. Int J Chron Obstruct Pulmon Dis. 2014;9:1163-1186.
19. Roche N, Postma DS, Colice G, et al. Differential effects of inhaled corticosteroids in smokers/ex-smokers and nonsmokers with asthma. Am J Respir Crit Care Med. 2015. In Press.
20. Fairfax, A., Hall, I., Spelman, R. A randomized, double-blind comparison of beclomethasone dipropionate extrafine aerosol and fluticasone propionate. Ann Allergy Asthma Immunol. 2001;86:575–582.
21. Asthma Initiative for Michigan (AIM). Asthma Predictive Index. Available online at: http://getasthmahelp.org/asthma-predictive-index.aspx (last accessed 2 June 2015)
22. Guilbert TW, Morgan WJ, Krawiec M, et al on behalf of the Childhood Asthma Research and Education Network. The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. Control Clin Trials. 2004;25:286-310.

APPENDIX

OPCRD data dictionary

1. Patient

The **Patient** file contains basic patient demographics, patient registration and practice registration details.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Practice_ID	Unique practice identifier.
Year_Of_Birth	Patient year of birth in format YYYY
Gender	Patient gender
Status	Patient registration status - (R) – Registered, (L) – Left, (D) - Death
Joined_Date	Date joined practice or date first registered on database
Leaving_Date	Date left practice or date first registered on database
Leaving_Reason	Reason for leaving practice
Post_Code	"Out" part of patient postcode and first character of "in" part of patient post code

2. Clinical

The **Clinical** file contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allows linkage of codes to the medical terms provided.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Numeric_1	First numeric value if stored
Numeric_2	Second numeric value if stored
Text	First 50 characters of any text associated with entry

3. Referral

The **Referral** file provides details of all referrals for the defined patient cohort identified by a medical code indicating the reason for referral. This table contains information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care).

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Read_Code	Five byte read code for event including terminal code if available
Read_Term	Rubric associated with read_code
Referral_Type	Referral type e.g. Outpatient

Referral_To	Organisation referred to
Specialism	Referral by e.g. GP referral
Attendance_Type	Attendance type e.g. First visit, follow up

4. Therapy

The **Therapy** file contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the Multilex product code system.

Field Name	*Content*
Patient_ID	Anonymised patient identifier
Event_Date	Date of event in format dd/mm/yyyy
Drug_Code	Coding for drug
Drug_Term	Drug term associated with drug code
Form	Formulation e.g. inhaler, tablets etc
Dosage	Usage instructions
Quantity	The quantity supplied
numberpack	Number of packs prescribed
packsize	The units of quantity supplied. (the preparation)
issue_ty	Type of issue where A = Acute Issue, R = Repeat Issue
strength	Drug strength
numberdays	Treatment days
bnf_code	BNF code

5. Practice

The **Practice** file contains details for practices, including region and collection information.

Field Name	*Content*
PracticeID	Unique OPC practice id
Practice_NHS	Unique NHS practice identifier.
Practice_Name	Name of practice
Practice_Address1	Address line 1
Practice_Address2	Address line 2
Practice_Address3	Address line 3
Practice_Address4	Address line 4
Practice_Postcode	Post Code
Practice_list_size	Total practice list size
Last_Extract_Date	Date when practice last did an extract