RESEARCH IN REAL LIFE LTD STUDY PROTOCOL
INCREASING ICS DOSE vs. ADD ON THERAPY IN CHILDREN WITH ASTHMA

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OPTIMUM PATIENT CARE

Optimum Patient Care (OPC) is a not-for-profit social enterprise division of Research in Real Life (RiRL) led by clinical academic, Professor David Price. We are committed to promoting best practice in chronic disease management delivered in primary care and have developed the OPC clinical review service to support general practices in this aim. An additional benefit of the clinical review services is the ability to identify specific patient groups that are the most likely to be appropriate for recruitment to research and clinical trials.

Ethical approval for the study is provided by the Scientific and Ethical advisory group linked to CPRD.

STUDY OBJECTIVE

Primary Objective

Step-up

The primary focus is to investigate the relationship between a step-up in asthma treatment (i.e. addition of a long-acting β-agonist (LABA), leukotriene receptor antagonist (LTRA) or increased ICS dose) in children aged 5-12 and the impact on asthma control over a 12 month period.

Secondary Objective

Change in device

As a secondary objective, the study will also investigate the relationship between change in inhaler type on the same therapy dose (e.g. DPI to MDI, DPI to MDI) and the impact on asthma control over a 12 month period.

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STUDY DATA SOURCE

The analysis will be carried out in an extended dataset comprising pooled primary care data from the Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD) to maximize patient numbers for the study, thus increasing GPRD data.

CPRD utilises anonymised individual patient clinical and prescribing data routinely collected by UK general practitioners subscribing to the Clinical Practice Research Datalink (CPRD), a large well validated UK database extensively used in pharmaco-epidemiological studies.

Similar to the CPRD, the Optimum Patient Care Research Database (OPCRD) also comprises of anonymised data extracted from practices supplemented by patient-reported outcomes collected via a questionnaire.. OPCRD data collection occurs during clinical reviews of practices' chronic respiratory services. The OPCRD has been approved by Trent Multi Centre Research Ethics Committee for clinical research use and enables research to be carried out across a broad-range of respiratory areas.

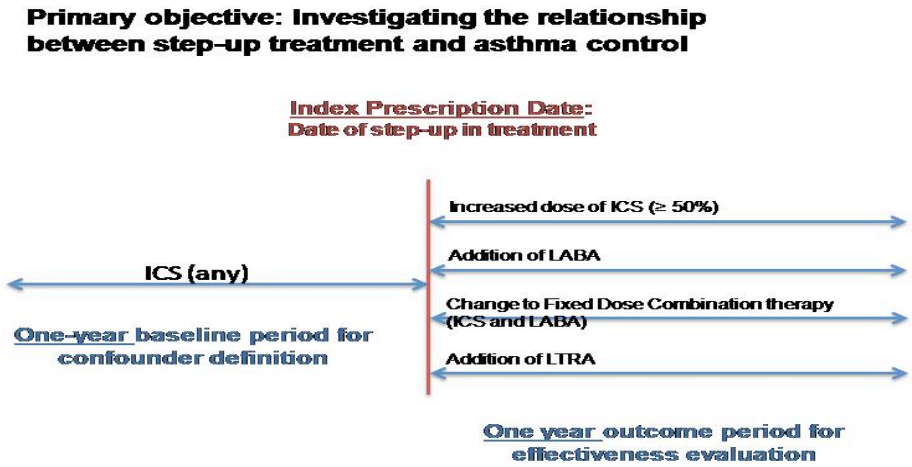
STUDY DESIGN

This is a retrospective, observational database study of real-world effectiveness, consisting of a baseline period, and outcome period and an index prescription date (IPD) at which asthma patients on inhaled corticosteroid therapy (any ICS) underwent either:

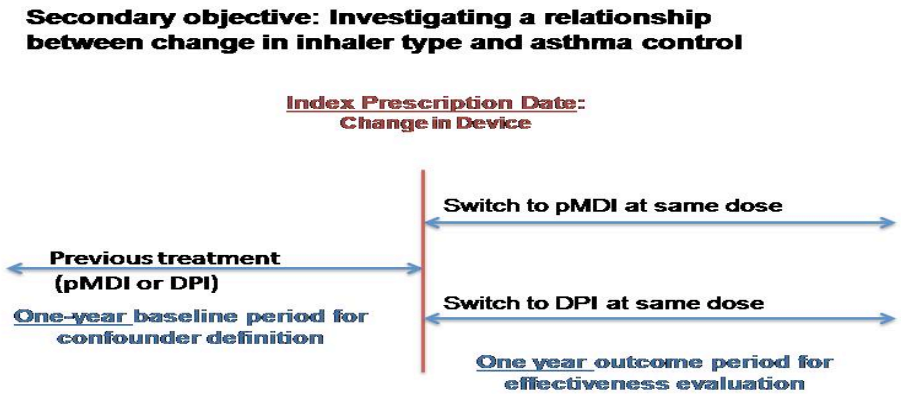
(i) An increase in ICS (at least 50% of prescribed dose);
(ii) A change to combination therapy by either:
- addition of a separate LABA, or
- change to a fixed-dose combination therapy;

(iii) Received LTRA as an addition to their current ICS therapy.
(iv) A change in device from pMDI to DPI or DPI to pMDI at same dose.

The baseline period will be a minimum of one year ?where treatment remains unchanged? before the IPD and will be used for confounder definition. The outcome period will be one year following the IPD.



To explore the outcomes of the secondary objective, the index prescription date will be taken as the date inhaler therapy was changed from one device to another for patients remaining on same therapy dose. During the outcome period, the cohorts on different inhaler devices can be compared over a one-year period for effectiveness and optional cost-effectiveness.



STUDY PERIOD

The study period will be between January 1990 (when all study therapies were available for prescription) and the end of December 2010 (2011). Patients included in the analysis will have been registered for at least one year prior to, and post, the IPD (when their asthma maintenance therapy – involving ICS and prn SABA – was changed). A one-year period is estimated to be necessary to

effect any measurable change in outcomes, such as hospitalisations, and to allow for seasonal changes in respiratory disease and its related conditions.

Outcome will run from months 0-12.

STUDY POPULATION

The analysis will include patients who underwent an increase in ICS or who were changed to combination ICS/LABA therapy, either as fixed-combination inhalers or separate ICS and LABA inhalers or received LTRA as an add on to their current ICS therapy at the IPD.

Inclusion criteria

- Aged: 5 - 12 years at index date;
- A medical diagnosis of asthma AND 2 or more therapies prescribed for asthma documented during the period 01/01/1990 to 31/12/2010 OR Two or more therapies prescribed for asthma documented during the period 01/01/1990– 31/12/2010. (GPRD selection criteria).
- Evidence of asthma: i.e. a diagnostic code of asthma or at least 2 asthma prescriptions, including one ICS prescription, at different points in time during the baseline year.
- Be on Active asthma therapy: i.e. 2 asthma prescriptions, including one ICS prescription, at different points in time during the baseline year.
- Have at least one year of up-to-standard (UTS) baseline data (prior to the IPD) and at least one year of UTS outcome data (following the IPD).

Exclusion criteria

Patients will be excluded from the analysis if they:

- Had any chronic respiratory disease, except asthma, at any time; and/or
- Patients on maintenance oral steroids during baseline year;
- History of cystic fibrosis;
- Patients receiving combination inhaler in addition to a separate ICS inhaler in baseline.

Matching criteria

Patients will need to be matched on key demographic and asthma-related characteristics during the baseline year to ensure similarity of patients. To ensure the comparison of like patients, individual patients in the two treatment arms will be matched on important baseline clinical characteristics. 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
- Exacerbations, split with antibiotics and without antibiotics
- Asthma consultations not resulting in an oral steroid prescription (i.e. avoids colinearity with outcome above)
- Baseline SABA usage
- Average daily ICS dose (within categories computed based on baseline usage)
- For objective 2 only: medication type

EXPOSURES, OUTCOMES AND COVARIATES

Exposures

The following exposures will be compared:

a. Whole-cohort analysis: Primary Objective:
   Patients receiving ICS therapy who underwent one of the following therapy changes at IPD (see summary table below):
   a. Increased ICS dose by at least 50%;
      At this stage is it possible to identify wheher the increase was from low (ie up to 200 microg BUD or equivalent) to intermediate dose (ie 201-400 microg) OR intermediate to high dose (ie >400 microg/day)
   b. Received LABA by either:
      i. addition of a separate LABA, or
      ii. change to a fixed-dose combination therapy.
   c. Received LTRA as addition to current ICS therapy.

b. Secondary Ojective
   Patients receiving ICS therapy with a pMDI or DPI who changed their inhaler to either a DPI or pMDI respectively at the same dose. Will we have information on spacer prescription too?? Change from MDI/spacer to MDI alone and vice versa would be interesting (anticipate problem in identifying spacers as these are not prescribed as regularly as inhalers)

Baseline therapy	**Therapy change at index prescription date (IPD)**							
ICS (any)	**Increased ICS** (≥50%)	OR	**Original ICS* + LTRA**	OR	**Original ICS* + LABA**	OR	**Fixed dose combination*** *	BDP/FOR (Fostair)
								FP/SAL (Seretide)
								BUD/FOR (Symbicort)

Study Outcomes

(1) Primary Effectiveness outcome

Exacerbation Rate (ATS/ERS Definition)

Where an exacerbation is defined as the occurrence of:

(i) Asthma-related[1]:
   a. Hospital attendance / admissions OR
   b. A&E attendance

(ii) Use of acute oral steroids[2]

(2) Secondary Effectiveness outcomes

(2a) **Risk Domain Asthma Control** (a composite proxy measure) defined as the absence of exacerbation and the absence of antibiotic prescribing for lower respiratory tract infections (often a pragmatic prescribing decision taken by GPs in real world practice).

Controlled: the absence of the following during the one-year outcome period:

(i) Asthma-related[1]:
   a. Hospital attendance or admission
   b. A&E attendance, OR
   c. Out of hours attendance, OR
   d. Out-patient department attendance

(ii) GP consultations for lower respiratory tract infection

(iii) Prescriptions for acute courses of oral steroids[2]

Uncontrolled: all others.

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[1] Asthma-related includes all events with a **lower respiratory code**, i.e. all asthma and lower respiratory tract infection codes

respiratory tract infection codes

[2] Where:

≥1 oral steroid prescription occurs within 2 weeks of another, or

(2b) **Exacerbation Rate (Clinical Definition):**

Where an exacerbation is defined as the occurrence of:

(i) Asthma-related[1]:
- a. Hospital attendance / admissions OR
- b. A&E attendance

(ii) Use of acute oral steroids[2]

(iii) GP consultations for lower respiratory tract infection.

(2c) **Overall Asthma Control (Risk Domain & Impairment):**

Controlled: the absence of the following during the one-year outcome period:

(i) Asthma-related[1]:
- a. Hospital attendance or admission
- b. A&E attendance, OR
- c. Out of hours attendance, OR
- d. Out-patient department attendance

(ii) GP consultations for lower respiratory tract infection

(iii) Prescriptions for acute courses of oral steroids[2]

(iv) Average prescribed daily dose of albuterol or terbutaline of ≤200mg.

Uncontrolled: all others.

(2d) **Treatment Success**

Successful: the absence of the following during the one-year outcome period:

(i) Asthma-related[1]:
- a. Hospital attendance or admission
- b. A&E attendance, OR
- c. Out of hours consultations, OR
- d. Out-patient department attendance

(ii) GP consultations for lower respiratory tract infection

(iii) Prescriptions for acute courses of oral steroids

(iv) No additional or change in therapy:
- a. Increased dose of ICS (≥50% increase), and/or

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[2] Where:
≥1 oral steroid prescription occurs within 2 weeks of another, or
≥1 hospitalisation occurs within 2 weeks of another, or
≥1 hospitalisation occurs within 2 weeks of an oral steroid prescription
These events will be considered to be the result of the same exacerbation (and will only be counted once)

b. Use of additional therapy as defined by: theophylline and leukotreine receptor antagonists (LTRAs).

Unsuccessful: all others.

(2e) **Hospitalisations**

Asthma-related hospitalizations[1]:

a. **Definite**: Hospitalisations coded with a lower respiratory code
b. **Definite + Probable**: Hospitalisations with an asthma read code + uncoded hospitalisations occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory read code

(2f) **Adherence** to ICS therapy (based on prescription refills) categorised as: <50%, 50-<70%, 70-<100%, ≥100%.

(2g) **SABA usage**: average daily dosage during outcome year.

(2h) **Oral thrush :** Identified as:

(i) Topical oral anti-fungal prescriptions, and / or

(ii) Coded for oral candidiasis

Covariates

Prior research in respiratory disease has identified a range of potential confounders that may impact on study outcomes. These include a range of demographic, disease severity, treatment and co-morbid factors. These variables will be extracted, where available, for all patients.

Potential confounders examined at (or closest to) the relevant index date:

- Age of patient
- A marker of socio-economic status where possible, i.e. post codes
- Gender of patient
- Height of patient
- Weight of patient
- Body Mass Index (BMI) (in sub-group where BMI can be evaluated)
- Lung function, in terms of percent predicted PEF[3] prior to index date
- Change of inhaler type

Potential confounders examined regardless of when they occurred relative to the index date:

- Date of first asthma diagnosis

[3] Calculated using Roberts' Equations for adults and Rosenthal's Equations for paediatrics (and incorporating Robinson's Equation for paediatrics ≤1.1m tall).

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- Other respiratory or other confounding diagnoses, including: rhinitis and / or eczema

Potential confounders examined in the year before AND year after the index date:

- Number of general practice consultations for asthma or other respiratory illness
- Number of hospital outpatient attendances where asthma is recorded as the reason for referral
- Number of hospitalisations for asthma or possibly respiratory related (a non-specific hospitalisation code and an asthma / respiratory code within a one week window).
- Number of prescriptions for any antibiotic where the reason for the prescription is a LRTI.
- Short-acting beta-agonist (SABA) usage
- Average ICS daily dose during baseline year (matching criteria, so only to be adjusted for in unmatched analysis)
- ICS dose at index date
- Spacer prescribing.

Code lists

Code lists using OXMIS, Read and drug have been developed by the researchers who include part-time academic GPs. They have developed and refined these over the last 3 years in their own research, and in collaboration with other academic partners, in a large number of primary care database studies. The CCI has been developed using ICD-9 matching algorithms produced by CLUE.

Statistical analysis

A statistical analysis plan with final comparators, age groups studied and approach of adjustment or matching will be determined by the study Steering Committee after a review of the baseline data.

Please refer to Research in Real-Life: Standard operating procedure (SOP) for observational, database studies in the appendix for further details.

LIMITATIONS OF THE STUDY DESIGN, DATA SOURCES AND ANALYTICAL METHODS

As with all database studies, a number of limitations existed for which it was not possible to adjust (e.g. potential confounding factors with the problem of internal validity).

The methods of adjustment that will be used will addressed all factors for which it is possible to account. Given the inherent limitations of database studies, however, the study results need to be

viewed in conjunction with those of other study designs, in particular RCTs, which (in respiratory disease) suffer from low external validity.