# **Title**: Real-life effectiveness (and cost impact) evaluation of fixed-dose combination fluticasone propionate/formoterol (Flutiform®) for the management of asthma in a routine UK primary care population – Phase 2

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

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## Objective

To evaluate the effectiveness (and cost impact) of changing real-life asthma patients from fluticasone propionate / salmeterol (Seretide®; FP/SAL) to fluticasone propionate / formoterol (Flutiform®; FP/FOR).

## Background

Asthma is one of the most common chronic diseases, with an estimated 300 million sufferers worldwide [1]. In addition to its effect on quality of life (of 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]. In patients whose asthma is not adequately controlled by ICS alone, the current Global Initiative for Asthma (GINA) guidelines recommend the addition of a LABA as a valid step-up option [4]. The combination of ICS and LABA provides both anti-inflammatory and bronchodilatory effects. Data suggest that combination ICS/LABA therapy is most effective when delivered as a *fixed dose* combination (FDC) inhaler, probably due to simplicity of dosing and improved patient adherence [5].

Optimising medication adherence is a challenge in chronic disease management, but it is believed that the addition of LABA to ICS may improve adherence, in part, because the bronchodilator's effect may afford symptom relief and enhance patients' perception of their treatment's efficacy. It is hypothesised that the faster the onset of action of the LABA in a FDC, the more rapid the symptom relief the patient may experience and, hence, the greater their perception of medication benefit. To this end, combining the anti-inflammatory effects of FP with the rapid-onset bronchodilatory effects of formoterol [6], as used in FP/FOR, may provide more rapid symptom relief than combining FP with the slower-acting LABA salmeterol (i.e. as in Seretide). A recent study demonstrated that up to 40% of the patients were found activating an empty or near empty MDI resulting in sub-optimal therapy [7]. Hence, a dose counter like in Flutiform® will be advantageous in improving patient compliance. In addition, fine particle size was found to have a positive impact on lung deposition [8]. On the same line of real-life benefits, Flutiform® was found to provide a consistent fine particle fraction of approximately 40% of the delivered dose [9, 10]. These practical designs of FP/FOR together with the rapid symptom relief of formoterol may add to better asthma management.

This hypothesis is supported by early randomized controlled trial (RCT) data that suggest FP/FOR is as effective as FP/SAL, but achieves more rapid bronchodilation [11, 12]. Further longitudinal studies are required with FP/FOR to ascertain the implications of this rapid-action bronchodilation in terms of improved adherence and effectiveness when used in real-life clinical practice.

## Hypotheses

Owing to the hypothesised enhanced adherence to their FDC ICS/LABA due to the fast action of formoterol, patients prescribed FP/FOR will achieve outcomes at least as good as patients prescribed FDC FP/SAL. The clinical benefit of improved adherence and overall

asthma control management afforded by FP/FOR may also be discernible in terms of reduced overall asthma-related costs.

## Data Source

### *Optimum Patient Care Research Database*

The Optimum Patient Care Research Database (OPCRD) comprises anonymised data extracted from practices receiving Optimum Patient Care's chronic respiratory service evaluation. Two types of anonymised patient data are typically collected:

(i) 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.
(ii) Patient reported outcomes: Eligible respiratory patients (e.g. those with diagnoses and/or in receipt of prescriptions for obstructive lung disease and approved for participation by the practice GP) are invited to complete validated disease assessment questionnaires to capture patient reported data on disease status and (where present) possible reasons for sub-optimal control/disease status.

See Appendix 1 for further information regarding the creation of the study dataset.

## Study Design

**Methodology**

This will be a matched retrospective, observational database study with a baseline and outcome period designed to evaluate the effectiveness (absolute and compared with FDC FP/SAL) and cost impact of initiating FDC ICS/LABA as FP/FOR or changing to FP/FOR from existing FP/SAL.

**Study periods**

The study period will run from one year before the UK FP/FOR launch through to 2 years post launch, comprising a baseline period, an index prescription date and an outcome period.

Index prescription date

**Change cohort:** For those patients changing to FP/FOR from existing FP/SAL the IPD will be the date for their first FP/FOR prescription. For patients in the control arm, i.e. those who continue on FP/SAL therapy, the IPD will be defined as the date of prescription issuance closest to the IPD of their matched FP/FOR counterparts.

Baseline

The **baseline period** will be the one-year period immediately prior to the IPD, during which patients will be characterised in terms of demography, clinical characteristics and asthma severity.

Outcome Periods

Outcomes for this Phase 2 study will be evaluated as follows:

12 months post IPD (evaluated 18 months post FP/FOR's UK launch). Effectiveness and cost impact will be evaluated and compared between the baseline and outcome years for patients changing to FP/FOR from FP/SAL.

## Exposures and Outcomes

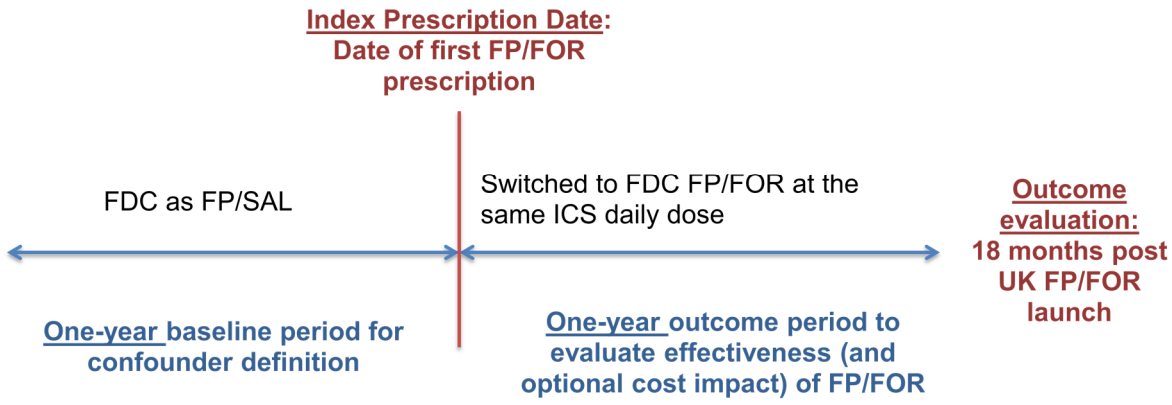
### General

- FP/FOR patients receiving prescriptions for any of the following formulations twice-daily will be eligible for inclusion: 100:10µg, 250:10µg and 500:20µg.
- FP/SAL patients will be eligible if they are receiving therapy via either pressurised metered-dose inhaler [pMDI; Evohaler®] or dry powder inhaler [DPI; Accuhaler®])

### Outcome periods

**Phase 2**: Pre and post IPD outcome evaluation (at 18 months post UK FP/FOR launch) in patients who, at IPD, change from existing FDC ICS/LABA therapy to FP/FOR and in whom there is ≥12-months of clinical data available post IPD.

**12-month effectiveness (and optional cost impact) evaluation of FP/FOR switch**



## Study population

***Inclusion criteria:***

**To be included in the study dataset, patients must also meet the following inclusion criteria:**

(i) Aged: 12–80 years

(ii) Evidence of active asthma, defined as a diagnostic code and/or ≥2 prescriptions for asthma therapy during the baseline year. For patients included in the matched 12-month comparative evaluation:
- **Initiation cohort:** patients must have received ≥1 ICS prescription during baseline.
- **FDC change cohort:** patients must have received ≥1 FDC prescription during baseline.

(iii) **Evidence of continued asthma treatment *in patients evaluated 12-months post IPD only***: ≥2 FP/FOR prescriptions during the outcome period

(iv) **Continuous records:**
- **For patients evaluated over the 12-month outcome periods:** at least one year of baseline data and at least one year of outcome data.

(v) All FP/FOR patients must be registered at practices considered to have a policy of FP/FOR adoption or wholesale change. Such practices will be identified as those at which ≥5 patients initiate on FP/FOR or change from existing FDC ICS/LABA (any) therapy to FP/FOR within a three-month period.

***Exclusion criteria:***

**Patients will be excluded if they:**

(i) Have a diagnosis for any chronic respiratory disease diagnosis, except asthma, at any time; and/or

(ii) Received maintenance oral steroids during the baseline year, and/or

(iii) Received multiple FDC ICS/LABA or separate ICS or LABA prescriptions at IPD[a].

## Outcome evaluation

Outcomes will be evaluated at three time points:

(i) **Phase 2**: 12 months immediately post IPD[b] at which point pre and post IPD asthma control outcomes (and optional cost impact) will be evaluated for patients changing from existing FDC ICS/LABA therapy to FP/FOR.

**Outcome measures**

**Phase 2:** The following asthma control and (optional) cost impact outcomes will be evaluated and compared between the pre- and post-IPD years for patients changing from FP/SAL to FP/FOR at IPD.

***Asthma control outcomes***

[a] Multiple prescriptions mean it is not possible to accurately calculate the FDC ICS/LABA dose at point of initiation or change

[b] The two 12-month outcome analyses will be performed ~18 months and the 24-months post FP/FOR's UK launch

## Co-primary outcomes

**1. Severe exacerbation rate (ATS/ERS definition)**
*Defined as any of the following during outcome year:*
- Asthma-related hospital or emergency room attendance
- Acute oral steroid prescriptions for asthma

**2. Composite proxy asthma control**
*Defined as absence of the following during the outcome year:*
- Severe exacerbations (as defined above)
- GP consultations for LRTIs[c].

## Secondary outcomes

**1. ICS use – mean daily ICS dose**: total ICS dose collected over the outcome year (based on prescription refills) divided 365 days.

**2. Short-acting beta$_2$agonist (SABA) use – mean daily SABA dose:** total SABA dose collected over the outcome year (based on prescription refills) divided by 365 days.

***Cost impact outcomes (optional)***

1. **Asthma drug costs ± FDC ICS/LABA drug costs:** ICS/LABA, ICS, SABA, LABA, leukotriene receptor antagonists, antibiotics for LRTIs and theophylline
2. **Cost of asthma resource utilisation:** combined and disaggregated GP consultations; A&E attendance; Out of hour services, Out Patient Department attendance; hospital admission coded for asthma
3. **Cost of asthma-related resource utilisation:** combined and disaggregated GP consultations; A&E attendance; Out of hour services, Out Patient Department attendance; hospital admission with a lower respiratory read code.

***Cost impact outcomes (optional)***

1. **Asthma drug costs ± FDC ICS/LABA drug costs:** ICS/LABA, ICS, SABA, LABA, leukotriene receptor antagonists, antibiotics for LRTIs and theophylline
2. **Cost of asthma resource utilisation:** combined and disaggregated GP consultations; A&E attendance; Out of hour services, Out Patient Department attendance; hospital admission coded for asthma
3. **Cost of asthma-related resource utilisation:** combined and disaggregated GP consultations; A&E attendance; Out of hour services, Out Patient Department attendance; hospital admission with a lower respiratory read code.

## Standard Definitions

### Asthma-related

The term “asthma-related” includes all events with a **lower respiratory code**, i.e. lower respiratory codes include all those for asthma and LRTIs.

[c] Asthma control extends the severe exacerbation definition to include antibiotics prescriptions for LRTIs on the rationale that, in routine practice, asthma exacerbations may be misdiagnosed and treated as LRTIs. Past work by RiRL has shown the asthma control outcome to be sensitive to changes in therapeutic management, hence support its use.

## Oral Steroids

### (a) Maintenance oral steroids

Where maintenance therapy is defined as daily dosing instructions of ≤10mg prednisolone or prescriptions for 1mg prednisolone tablets.

### (b) Acute oral steroids

Acute oral steroid use associated with asthma exacerbation treatment are defined as:

- All courses that are definitely not maintenance therapy, and
- All courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg "as directed"), and
- All courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or
- No or undefined dosing instructions but definitely not maintenance therapy.

## Unique exacerbations

Events will be considered to be the result of the same exacerbation (and will only be counted once) 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.

# Statistical Analysis

The statistical analysis plan will be discussed in full by the Steering Committee before analysis begins. As this is a long-term ongoing study; the analysis for phase 3 is likely to be informed by the results of phase 1.

General

Statistically significant results will be defined as $p<0.05$ and trends as $0.05 \leq p<0.10$.
All analyses will be carried out using SPSS version 19 [13], SAS version 9.3 [14] and Microsoft Office EXCEL 2007.

Summary statistics

Summary statistics will be produced for all baseline and outcome variables, as a complete dataset and by treatment groups. For variables measured on the interval or ratio scale, these will include:

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

For categorical variables, the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution)

Matching and statistical modelling

Matching will be performed to provide a more robust analysis with matching criteria selected as appropriate and informed by cohort characterisation through a combination of categorical and continuous demographic and clinical variables. Any residual differences remaining after matching that are considered to be significant between the treatment arms, or predictive of outcomes, will be considered as potential confounders and will be adjusted for through conditional regression modelling.

Patients will be match on key demographic and disease severity characteristics. The exact matching criteria will be defined following baseline cohort characterisation, but are expected to be:

(i) Age
(ii) Gender
(iii) Short-acting beta agonist use (SABA) – mean daily dose
(iv) Number of oral steroid courses (e.g. 0, 1, ≥2)
(v) Baseline ICS dose (either last prescribed or mean daily as optimises number of matched pairs)
(vi) Number of asthma consultations not resulting in an oral steroid course (e.g. 0, 1, ≥2)
(vii) Date of IPD ± 3 months.

## Covariates

Prior research in respiratory disease has identified a range of potential confounders that may affect study outcomes. These include a range of demographic, disease severity, treatment and co-morbid factors. Initial analysis will identify the key baseline confounders, and outcome analyses will take these findings into account and select appropriate statistical methods to minimise potential confounding. 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)
- Ethnicity
- Lung function, in terms of percent predicted PEF[d] prior to index date
- Smoking status
- ICS or ICS/LABA device type

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

- ICS drug

**Potential confounders examined in the year prior to the index date or ever:**

- Date of first asthma diagnosis
- Duration of asthma
- Presence / absence of comorbid rhinitis
- Where rhinitis is present, use of nasal steroids for its treatment.
- Presence / absence of comorbid eczema
- Other important unrelated co-morbidities will be expressed using the Charlson Comorbidity Index (CCI)
- Presence of GERD
- Presence of cardiac disease
- Number of asthma consultations that did not result in a prescription for an oral steroid
- 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 reason for the prescription is LRTI
- Other medications that might interfere with asthma control:
- Number of paracetamol prescriptions in prior year.
- Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescribed in the prior year
- Number of beta-blocker prescriptions in prior year
- Number of prescriptions for any respiratory therapy (split by number of prescriptions for each) in the prior year
- Number of exacerbations for asthma in year preceding assessment (exacerbation defined above)
- Number of general practice consultations for asthma that did not result in asthma exacerbations treatment and / or other respiratory illnesse antibiotics in prior year.
- Number of hospital outpatient attendances in the prior year where asthma and / or other respiratory illness was the reason for referral.
- Number of hospitalisations for asthma and / or respiratory illness in the prior year (including non-specific hospitalisations with an asthma / respiratory code within a one week window).
- Number of prescriptions for any antibiotic in the prior year where the reason for the prescription is lower-respiratory tract infection.
- Number of short-acting beta-agonist (SABA) prescriptions received in the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days).
- Average ICS daily dose during the prior year (calculated based on total combined dose of refilled prescriptions and averaged over 365 days).
- ICS dose prescribed at index date.
- Spacer use / prescription.
- First or subsequent change (i.e. ≥second change) change of ICS/LABA drug
- First or subsequent step up (i.e. ≥second step-up) from ICS to ICS/LABA dose.

## Sample Size and Power Calculations

**Phase 2**

Based on an assumed probability of "no exacerbations" of 0.82 and allowing a probability of no exacerbations to fall to 0.695, but no further, to indicate "non-inferiority" in terms of exacerbation control of change to FP/FOR from FP/SAL, a total of 154 FP/FOR patients would be required.

This population size is based on the FDC ICS/LABA exacerbation rate recorded by the RiRL team in a recent UK study and uses the McNamara Test for a one-sided test of equality (i.e. non-inferiority), allowing a probability of no exacerbations to fall to from 0.82 to 0.695 (i.e. to the point that 30.5% have ≥1 exacerbation). Based on these assumptions, a sample size of 154 pairs will have 90% power to detect a difference in proportions of 0.125 when the proportion of discordant pairs is expected to be 0.300 and the method of analysis is a McNamara's test of equality of paired proportions with a 0.050 one-sided significance level.

## Limitation of the study design, data sources and analytical methods

As with all real-life database studies, a number of limitations will exist using the real-life OPCRD datasets 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 Napp Pharmaceuticals, as the study sponsor.

## Researcher Team

**Chief Investigator**: Professor David Price, Professor of Primary Care Respiratory Medicine and Director of Research in Real Life

Steering Committee

**Confirmed names:** Ian Small, Kevin Gruffydd-Jones, John Hamill, Cathal Daly and Stephanie Wolfe

Research Team: Research in Real Life

**Catherine Hutton:** Chief Executive, Research in Real Life

**Victoria Carter**: Project Coordinator, Research in Real Life

**Daina Lim:** Researcher, Research in Real Life

**Annie Burden:** Senior Statistician, Research in Real Life

**Julie von Ziegenweidt:** Data Analyst, Research in Real Life

Study Sponsors: Napp Pharmaceuticals

**Primary Contact:** Rupert Roe

## Timetable and Delivery

The estimated timings of the study phases are according to a UK FP/FOR launch date of **September 2012,** with actual first prescription dated Nov 2012.

Total timeframe from project go-ahead to Phase 3 manuscript development will be 40 months, i.e. based on a September 2012 launch date, the aim will be to complete the Phase 3 manuscript draft by the beginning of January 2016.

For a schematic representation of the study timeline, see the project timeline and costing Excel file: "**Flutiform change study_timeline and costing_4th May 2012.xlsx**"

| Study Phase | Study element | Start date | Completion date |
|---|---|---|---|
| **Phase 1** (6-month FP/FOR outcome evaluation) | **Phase 1 study site identification** | Sep 2012 | Jul 2013 |
| | **Phase 1 data extractions** | Aug 2013 | Oct 2013 |
| | **Phase 1 analysis** | Nov 2013 | Dec 2013 |
| | **Phase 1 report delivery** | Jan 2014 | |
| | **Phase 1 Steering Committee Meeting** | Jan 2014 | |
| | **Phase 1 Data Dissemination (Congress Abstract/Poster)** | Feb 2014–May 2014 | |
| **Phase 2** (FP/FOR 12-month outcome evaluation; 18 months post launch) | **Phase 2 additional site identification** | Feb 2014 | Apr 2013 |
| | **Phase 2 data extractions** | May 2014 | Jul 2014 |
| | **Phase 2 analysis** | Aug 2014 | Oct 2014 |
| | **Phase 2 report delivery** | Nov 2014 | |
| | **Phase 2 Steering Committee Meeting** | Nov 2014 | |
| | **Phase 2 Data Dissemination (Congress Abstract/Poster)** | Dec 2014 | Mar 2015 |
| | **Phase 2 Data Dissemination (Manuscript development)** | Apr 2015 | May 2015 |
| **Phase 3** (matched FP/FOR vs FP/SAL 12-month outcome evaluation 24 months post launch) | **Phase 3 additional site identification** | Nov 2014 | Jan 2015 |
| | **Phase 3 data extractions** | Feb 2015 | Mar 2015 |
| | **Phase 3 analysis** | Apr 2015 | Jun 2015 |
| | **Phase 3 report delivery** | Jul 2015 | |
| | **Phase 3 Steering Committee Meeting 1** | Jul 2015 | |
| | **Phase 3 Data Dissemination (Congress Abstract/Poster)** | Jul 2015 | Oct 2015 |
| | **Phase 3 Steering Committee Meeting 2** | Oct 2015 | |
| | **Phase 3 Data Dissemination (Manuscript development)** | Nov 2015 | Dec 2015 |

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## APPENDIX 1: Dataset creation – cost- and time-impingent phases

***Background to the OPCRD***

Optimum Patient Care (OPC) is a science-led, social enterprise company committed to working with UK primary care practitioners to produce quality, focused patient profiles that make a difference to managed care. Led by internationally-recognised respiratory experts, OPC offers free respiratory service evaluations with a view to optimising the efficiency and effectiveness of primary care services, for the benefit of general practitioners and patients alike.

The OPC service evaluation combines records-based assessments with patient-reported questionnaire responses to evaluate the effectiveness of the current respiratory service being offered. All patient-level data collected by OPC is anonymised at point of extraction, but clinical records and patient reported outcomes can be cross-referenced through use of unique patient identifiers. Where appropriate, OPC makes recommendations for management changes (in line with best practice respiratory guidelines). All recommendations are returned to the practice for consideration and are only adopted at the discretion of the physician.

Anonymous service evaluation data is held in the OPC research database (OPCRD), which has been granted ethical approval for use in medical research by the Trent Multi-Ethics Research Committee.

***OPCRD and the FP/FOR change study***

As FP/FOR is not yet launched in the UK, there are currently no FP/FOR patient records within the current OPCRD. Data on FP/FOR patients will need to be prospectively collected (for retrospective evaluation) from practices intending, or interested, in nurse-led, or IT-, FP/FOR change programmes. OPC will identify these practices in collaboration with Napp representatives.

The lead time and costings for the Phase I, 2 and 3 analyses are based on the time and resource required to collect sufficient FP/FOR patient data to power the three, phased analyses. The cost and time-impingent study phases are summarised below. A detailed breakdown of the times and costs associated with each of the data collection, analysis, consultation and publication phases can be found in the Excel file: "**Flutiform change study_timeline and costing_4th May 2012.xlsx**"

<u>Prospective data collection</u>

Identification of FP/FOR change-eligible patients and subsequent changing will require the following activities from OPC staff:

- Practice visit to extract patient practice data
- Review of the practice dataset to identify patients eligible for change
- Practice visit to upload a "change prompt" (for eligible change patients) to practice computer

There will then be a lead-time before the changes are implemented. Changes may occur at the time of patients' next asthma reviews and/or repeat prescription, or (if agreed with the

practice and the study sponsor) at an OPC nurse-led clinic to which patients eligible for FP/FOR change will be invited and, after which, changes will take immediate effect.

Return practice visits to extract post change data for retrospective evaluation

- **Repeat visit 1**: 6 months post change (e.g. 6-months after the data of a nurse-led change clinic at participating practices) – to generate **Phase 1** study dataset
- **Repeat visit 2**: 12 months post change – to generate **Phase 2** study dataset
- **Repeat visit 3**: 18 months post change – to generate **Phase 3** study dataset

Analysis

Once the prospective data collection element of the study is complete, the research analysis will commence. The costs and timelines given account for the following analysis elements:

- Finalisation of the raw data extractions into the research-quality OPCRD dataset
- Identification of the study-specific patients data within, and extract from, the OPCRD
- Phase 1 data analysis
- Analysis of the unmatched data to identify appropriate matching criteria
- Matching of the Phase 3 patients
- Analysis of the matched data
- Review the data in collaboration with the independent steering committee
- Revise the analysis, as required, following steering committee input
- Data dissemination – congress level and/or peer-review journal manuscripts

## APPENDIX 2: Adverse events coding and identification

The OPCRD uses Read codes, hence all Read codes will be converted to MedDRA code and categorised by disease area (e.g. cardiovascular events, renal events) in line with the Read Code categorisations detailed below:

| READ CODE | READ TERM |
|---|---|
| **A....00** | Infectious and parasitic diseases |
| **B....00** | Neoplasms |
| **C....00** | Endocrine, nutritional, metabolic and immunity disorders |
| **D....00** | Diseases of blood and blood-forming organs |
| **E....00** | Mental disorders |
| **F....00** | Nervous system and sense organ diseases |
| **G....00** | Circulatory system diseases |
| **H....00** | Respiratory system diseases |
| **J....00** | Digestive system diseases |
| **K....00** | Genitourinary system diseases |
| **L....00** | Complications of pregnancy, childbirth and the puerperium |
| **M....00** | Skin and subcutaneous tissue diseases |
| **N....00** | Musculoskeletal and connective tissue diseases |
| **P....00** | Congenital anomalies |
| **Q....00** | Perinatal conditions |
| **R....00** | [D]Symptoms, signs and ill-defined conditions |
| **S....00** | Injury and poisoning |
| **T....00** | Causes of injury and poisoning |
| **U....00** | [X]External causes of morbidity and mortality |
| **Z....00** | Unspecified conditions |

***Adverse events classification***

Data will be extracted on **ALL** adverse events, serious or otherwise.

(a) Adverse events of **particular note** will include the following:[f]

(i) Local immunosuppressive effects, infections
(ii) Anaphylactic reactions
(iii) Psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression
(iv) Adrenal suppression
(v) Growth retardation
(vi) Decrease in bone mineral density
(vii) Cataract
(viii) Glaucoma

[f] Items (i)–(xi) have been identified as potential risks of FP/FOR treatment

(ix) Hypokalaemia
(x) Contusion
(xi) Skin atrophy
(xii) Hyperglycaemia / increased blood glucose
(xiii) Serious asthma-related events (asthma hospitalisations, intubations, deaths)
(xiv) Local oral adverse events
(xv) Adrenal failure
(xvi) Respiratory adverse events including paradoxical bronchospasm
(xvii) Cardiac arrhythmias
(xviii) Ischemia
(xix) All new events – i.e. the event occurs for the first time EVER in the patient's record after initiation of FP/FOR

(b) **Serious adverse events:** In line with the European Medicines Agency ICH Topic E 2 A publication on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* th[g]e following will be considered to be serious adverse events. Those that (at any dose):

(i) Result in death
(ii) Are life threatening[h]

[g] European Medicines Agency ICH Topic E 2 A publication on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. June 1995. Available online at:* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf (last accessed 4 August 2011)

[h] "life-threatening" refers to an event in which the patients was a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. The following are considered to have been "life-threatening", an event that: requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.