Impact of EU label changes for systemic diclofenac products: post-referral prescribing trends

Final Study Protocol

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Contents

1 BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, are widely prescribed agents across Europe for the management of pain, fever and inflammatory conditions. Systemic formulations of diclofenac containing medicinal products are available as tablets and capsules for oral administration, suppositories for rectal administration, and solutions for intravenous or intramuscular injection.

In June 2013, an EMA referral procedure was raised to the Pharmacovigilance Risk Assessment Committee (PRAC) to examine the cardiovascular safety of diclofenac based upon evidence from available randomised controlled trials and observational studies.[1-3] The referral procedure concluded that although diclofenac containing products are effective treatments for their approved indications, systemic formulations of diclofenac were associated with an elevated risk of acute cardiovascular events. The referral procedure concluded that in order for the benefit-risk balance of systemic diclofenac containing medicinal products to remain favourable, contraindications, warnings, and changes to the product information, including direct healthcare professional communication (DHPC) were required to be implemented across the EU.

The EMA implemented risk minimisation measures relating to the use of diclofenac in 2013. The main elements of this were that diclofenac should be:

- contraindicated in patients with congestive heart failure, ischemic heart disease, peripheral arterial disease &/or cerebrovascular disease
- cautioned in patients with certain cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus & smoking)
- used at the lowest dose for the shortest duration possible

As part of the PRAC strategy for measuring the impact of pharmacovigilance, the aim of this tender is to measure the effectiveness of regulatory actions taken for diclofenac containing medicinal products following the June 2013 referral conclusion. This will be assessed using four separate data sources: dispensed prescribing data from NHS Scotland (UK); prescribing from the Clinical Practice Research Datalink (UK); out-of-hospital prescriptions from the Danish Register of Medicinal Products (Denmark); and prescribing data from PHARMO Database Network (the Netherlands).

2 AIM

To evaluate the impact of the risk minimisation measures implemented in 2013 to manage the cardiovascular risks of systemic diclofenac containing medicinal products authorised in the European Union (EU) in clinical practice.

3 OBJECTIVES

Our objective is to describe the response to the DHPC, which drew attention to new contraindications, warnings, and other changes to the product information. We will analyse trends in prescribing patterns from a minimum of three years before the intervention for as long as each database allows (only 3½ years of data is available for analysis prior to the intervention in Scotland). We will provide these trends by indication for diclofenac, and by age and gender.

Our objectives fall into three areas:

3.1 OBJECTIVE 1: TO DETERMINE PRESCRIPTION PATTERNS OF DICLOFENAC CONTAINING PRODUCTS

We will include diclofenac-containing medicinal products with ATC (Anatomical Therapeutic Chemical) codes M01AB05 or M01AB55, and BNF (British National Formulary) codes 1001010AG or 1001010C0. This will identify:

- Systemic products formulated as tablets or capsules for oral administration (group 1)
- Suppositories for rectal administration (group 2)
- Solutions for intravenous or intramuscular injection (group 3)

For CPRD/PHARMO databases, diagnoses codes to identify clinical indications will be captured at the primary care level whilst for Scottish/Danish databases these codes will be captured within secondary care data consisting of outpatient and inpatient diagnoses data. Please see Appendix 1 for list of codes to define clinical indications within each database.

The primary analysis will calculate prescription patterns for overall diclofenac prescribing (based upon any type of diclofenac-containing product) starting at least three years before the regulatory intervention in:

1.1 diclofenac initiation rates
1.2 diclofenac prescribing rates by patients
1.3 diclofenac prescribing rates by prescriptions
1.4 diclofenac discontinuation rates
1.5 dose of diclofenac
1.6 duration of diclofenac therapy

This will first be done for any indication and then by indication, by age and by gender. Secondary analysis will calculate prescription patterns for each diclofenac-containing group (i.e. group 1 tablets/capsules, group 2 rectal suppositories and group 3 intramuscular/intravenous) for any indication and then by indication, age and gender

3.2 OBJECTIVE 2: DETERMINING PRESCRIBERS COMPLIANCE WITH CARDIOVASCULAR CONTRAINDICATIONS AND RISK FACTORS

We will assess compliance with recommendations included in sections 4.3 and 4.4 of the Summary of Product Characteristics for systemic diclofenac containing medicinal products by calculating prescription patterns in overall diclofenac prescribing rates and diclofenac initiation rates among patients with a history of:

2.1 congestive heart failure
2.2 ischemic heart disease
2.3 peripheral arterial disease
2.4 cerebrovascular disease
2.5 hypertension
2.6 hyperlipidaemia
2.7 diabetes
2.8 smoking

For overall diclofenac prescribing this will first be done for any indication and then by indication, age and gender.

Secondary analysis will calculate prescription patterns for each diclofenac-containing group (i.e. group 1 tablets/capsules, group 2 rectal suppositories and group 3 intramuscular/intravenous) for any indication and then by indication, age and gender.

3.3 Objective 3: Determine prescription patterns of alternative medicines prescribed in patients where diclofenac has previously been prescribed

Among patients who discontinue diclofenac therapy we shall calculate prescription patterns in the proportions who subsequently initiate treatment with:

3.1 Other systemic NSAIDs
3.2 Topical NSAIDs
3.3 Paracetamol
3.4 Opioids
3.5 Other chronic pain medication
3.6 None of the above

Please see Appendix 2 for list of codes used to identify these drugs.

4 Data source summaries

Four validated population data sources[4-9] will be used.

4.1 Scotland, UK

The Prescribing Information System (PIS) records all medicines dispensed from pharmacies in Scotland (population estimated 5.3 million in June 2014) and these can be record-linked using the person-unique Community Health Index (CHI) number to demographic data (e.g. age, sex, social deprivation, dates registered with family doctor), Scottish Morbidity Records (e.g. SMR01 – in-patient hospitalisations) and National Records of Scotland (NRS) death registrations for the entire population (International Classification of Diseases (ICD)-9/ICD-10 coded). Prescription data is available from 2009.[4]

4.2 Denmark

The Danish Register of Medicinal Products records all out-of-hospital prescriptions (full population coverage of 5.6 million individuals). A unique 10-digit personal identifier, the Centrale Person register (CPR) number,[5] readily allows linkage of drug exposures to outcomes in the form of ICD-10 diagnoses registered in connection with inpatient and outpatient hospital contacts.[6] Death data is available from the Civil Registration System. Prescription data is available from 1995.[7]

4.3 Clinical Practice Research Datalink (CPRD), UK

CPRD contains data originating from the computer systems of General Practitioners (GPs) across the United Kingdom with an estimated 6 million population. The data has been collected since 1987, it covers about 7% of the UK population and is broadly generalisable to the whole UK population.[8] For this study, data will be taken from all non-Scottish "up to standard" practices. Data on diagnostic coding and prescribing come from the GP system and are recorded as Read, Gemscript and BNF codes.

4.4 PHARMO DATABASE NETWORK, NETHERLANDS

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. To address the objectives of the present study the Out-patient Pharmacy and the GP Database will be used. The Out-patient Pharmacy Database of the PHARMO Database Network comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy (population 4.2 million in 2016). Dispensing data is available from 1998 and ongoing. These data can be linked on a patient-level using probabilistic linkage to other databases. Data on indication and contraindications are obtained from the GP Database for a population of approximately 1 million. This database comprises data from electronic patient records registered by GPs. Dispensing data is recorded as ATC and diagnoses as ICPC (International Classification of Primary Care) codes or entered as free text. ICPC codes can be mapped to ICD codes. [9]

5 STUDY METHODS

Population-based longitudinal studies will be conducted using these four databases using this common protocol that will be registered in the EU PAS (post-authorisation studies) Register.

5.1 OVERVIEW

Individual patient data sets will be assembled in each country and will not be transferred out of the country. The list of variables included in the study are defined in this document. Some of these variables are not available in every country. The different database structures and coding systems used by each country mean that different logic will be used to calculate each of the variables listed here. These will be reviewed for consistency between countries. To further improve consistency a high-level data extraction plan will be used, for each country to adhere to. An aggregate data set will be prepared in each country and forwarded to the study statistician providing the minimum count per time point contains greater than or equal to 5 patients per cell to meet with local data protection and disclosure control requirements. This will consist of a full cross classification of the data by all the stratification variables, and by time point.

5.2 STUDY PERIOD

The study period will start on 1/1/2006 for CPRD, Denmark and PHARMO and from 1/1/2009 for Scotland, when prescribing data is first available. The end of data collection will be 31/12/2016 or later where data are available.

5.3 STUDY POPULATION

The study population will consist of all patients registered within each data source at any time during the study period. The first follow-up date for a patient will be defined as date of registration with the general practice (CPRD and PHARMO), or date of first recorded prescription or any secondary care diagnosis (Denmark and Scotland). A patient's index date will be the latest of the study period start date (1/1/2006, or 1/1/2009 for Scotland), the date of birth, or their first database follow up date plus 1 year (to allow sufficient time for data on baseline covariates to be collected). A patient's last follow up date will be the first occurrence of the following: death (all databases); end of study period (varies between countries); end of registration (end of registration will not significantly affect data from Denmark and Scotland because they use national data that captures patients moving within the health system). A patient is included for analysis in a time period if the first and last day both lie between the patient's index date and their last follow up date, so the analyses will only include patients who are observable for the entire time period.

5.4 OUTCOME VARIABLES

For each of the objectives listed above we will analyse a series of proportions evaluated in each time point over the study period. The denominators are all patient counts. The numerators are either patient counts or numbers of prescriptions.

5.5 STRATIFICATION VARIABLES

Most stratification variables in this study are time dependent and will be evaluated at the start of each time period. Gender and age will be used to stratify diclofenac prescription rates for all three objectives.

Age will be classified as 0-17, 18-29, 30-39, 40-49, 50-59, 60-69, 70-79 or 80+.

Read, ICD or ICPC codes will be used to classify licenced indications: *Pain and inflammation in musculoskeletal disorders, Acute gout (and other crystal arthropathies)* and *Pain and inflammation in rheumatic disease, including juvenile idiopathic arthritis* which will be subdivided into osteoarthritis and other inflammatory arthropathies. The classification will be based on any record dated before the end of the time point.

5.6 OBJECTIVE 1: DEFINITIONS TO DETERMINE PRESCRIPTION PATTERNS OF DICLOFENAC CONTAINING PRODUCTS

5.6.1 Objective 1.1: Diclofenac initiation rates

Diclofenac initiation is defined as a prescription for diclofenac with no exposure to diclofenac in the preceding 92 days. Sensitivity analyses will be carried out with a non-exposure period of 180 days instead of 92 days. The denominator is the number of non-users on the first day of the time period defined as no exposure to diclofenac in the previous 92 days. The numerator is the number of these patients initiating diclofenac in the time period.

5.6.2 Objective 1.2: Overall diclofenac prescribing rates by patients

For overall diclofenac prescribing rates, the denominator is defined as the number of observable patients on the first day of the time period (both diclofenac users and non-users). The numerator is defined as the number of these patients with any prescription for diclofenac in the time period. The exception will be for Denmark where the denominator will be the number of patients present in the cohort on 1st January each year.

5.6.3 Objective 1.3: Overall diclofenac prescribing rates by prescriptions

Diclofenac prescribing rates will also be assessed at the prescription level among diclofenac users. The denominator is the number of patients prescribed diclofenac in the cohort in the time period. The numerator is the number of prescriptions they received.

5.6.4 Objective 1.4: Diclofenac discontinuation rates

Discontinuation is defined as the number of patients with a prescription for diclofenac with no exposure to diclofenac in the 92 days following the date of that diclofenac prescription. The denominator is the number of patients prescribed diclofenac in the time period. The numerator is the number of these patients discontinuing. Sensitivity analyses will be carried out with a 180 day time interval instead of 92 days.

5.6.5 Objective 1.5: Prescribed dose of diclofenac

This requires the calculation of an average total daily dose of diclofenac prescribed for each diclofenac-exposed patient during the time period. Average daily dose during a continuous treatment episode will be

calculated as (strength x quantity summed over all prescriptions in the episode) / (length of episode including unexposed days). This will allow the dose to be calculated from strength and quantity, and will be available for all data sources. Further details will be provided in the Data Extraction Plan.

5.6.6 Objective 1.6: Duration of diclofenac

From clinical experience we suspect most diclofenac prescribing will not be long term. The "as required" nature of NSAID prescribing and limited data to calculate duration in Denmark means estimating duration of prescribed therapy is challenging. Duration of treatment is this context is inherently difficult to decide, most use arbitrary definitions that may not accurately reflect real world use.

For the primary approach of estimating duration of diclofenac, we will assume a standard diclofenac treatment regimen for each patient and prescription as if they were taking it with complete adherence. For tablets/capsules we will use a total daily dose 150mg diclofenac. For example, a standard prescription consisting of 50mg strength tablets/capsules we will therefore divide the quantity of tablets/capsules per prescription by this standard regimen (i.e. 3) to provide the standard duration of therapy in days. We will measure trends in the average standard duration of therapy for prescriptions issued within each time period, before and after the date of the regulatory intervention.

As a secondary approach, we will attempt to divide patients prescribed diclofenac into one of three groups per time period: one-off users, sporadic users, and chronic users. One-off users will be defined as patients prescribed a single diclofenac prescription only. To define sporadic and chronic users we will calculate a possession ratio for each patient defined by using the number of days prescribed (or supplied) assuming a standard daily dose divided by the number of days between diclofenac prescriptions. We will define sporadic users as patients with a diclofenac possession ratio of less than 1 standard day of therapy per 3 days. Patients with a diclofenac possession ratio of more than 1 standard day of therapy per 3 days will be defined as chronic users. We will then calculate time trends for the three groups per time period, before and after the date of the regulatory intervention.

5.7 OBJECTIVE 2: DETERMINING PRESCRIBERS COMPLIANCE WITH CARDIOVASCULAR CONTRAINDICATIONS AND RISK FACTORS

Objective 2 requires stratification of the diclofenac prescription rates by each of the following factors with Read, ICD and ICPC codes listed in Appendix 3 for each condition.

5.7.1 History of congestive heart failure

Diclofenac is prescribed to the contraindicated group in a time period if any of the codes for congestive heart failure are recorded prior to the first day of that time period. Once recorded for a patient, they will continue to be considered contraindicated for all subsequent time periods.

5.7.2 History of ischemic heart disease

Diclofenac is prescribed to the contraindicated group in a time period if any of the codes for ischemic heart disease are recorded prior to the first day of that time period. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.7.3 History of peripheral arterial disease

Diclofenac is prescribed to the contraindicated group in a time period if any of the codes for peripheral arterial disease are recorded prior to the first day of that time period. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.7.4 History of cerebrovascular disease

Diclofenac is prescribed to the contraindicated group in a time period if any of the codes for cerebrovascular disease are recorded prior to the first day of that time period. Once recorded they will continue to be considered contraindicated for all subsequent time periods.

5.7.5 History of hypertension

A patient will be classified as hypertensive in a time period if any antihypertensive drug was prescribed prior to the start of that time period. Once recorded they will continue to be considered hypertensive for all subsequent time periods.

5.7.6 History of hyperlipidaemia

A patient will be classified as having hyperlipidaemia in a time period if any anti-hyperlipidaemic drug was prescribed prior to the start of that time period. Once recorded they will continue to be considered as having hyperlipidaemia for all subsequent time periods.

5.7.7 History of diabetes

A patient will be classified as having diabetes in a time period if any anti-diabetic drug was prescribed was prescribed prior to the start of that time period. Once recorded they will continue to be considered as be diabetic for all subsequent time periods.

5.7.8 Smoking history

The smoking status of patients in CPRD will be classified as current smoker, ex-smoker and never smoked using the most recent record prior to the start of each time period. In PHARMO, smoking status of patient will be classified as smoker, ex-smoker and never smoked using all smoking related examinations from a specified time window (e.g. one year prior to the start of each period) and then evaluated chronologically for each patient to assign the smoking status at the start of each time period.

For the analysis, we will calculate the proportion of patients prescribed diclofenac in each time period who have each of the above factors.

5.8 OBJECTIVE 3: DETERMINE PRESCRIPTION PATTERNS OF ALTERNATIVE MEDICINES PRESCRIBED IN PATIENTS WHERE DICLOFENAC HAS PREVIOUSLY BEEN PRESCRIBED

Objective 3 will determine drug utilisation and prescription patterns over time for other analgesics when diclofenac has been discontinued. Codes for each class of alternative analgesics are listed in Appendix 2.

A switch to an alternative class will be defined as those patients who have discontinued diclofenac (as defined in section 5.6.4) and who then initiate a drug in the classes listed in section 3.3. Initiation of an alternative drug in the classes listed in section 3.3 will be defined as the first prescription of a drug in that class prescribed within 92 days following the date of the last diclofenac prescription.

5.9 STATISTICAL ANALYSES

5.9.1 Time period definition

The primary analysis will use quarterly time periods. For each year these will be defined by the following dates:

- 1st January to 31st March = Quarter 1
- 1st April to 30th June = Quarter 2

- 1st July to 30th September = Quarter 3
- 1st October to 31st December = Quarter 4

Data governance requirements may preclude reporting of strata containing fewer than 5 patients. If this occurs we will either pool these strata with larger neighbouring groups (e.g. age 80+ with the 70-79 age group), or omit them. In either case, we will indicate in the report tables where data has been redacted.

5.9.2 Analytical approach

The proposed primary analysis will use interrupted time series regression to fit time trends to each series of time period data for each country. Using regression modelling we will evaluate:

1. The baseline slope before the intervention time point
2. The change in slope from the baseline trend to the post-intervention trend
3. The immediate change associated with the intervention time point

Before fitting all regression models, the data will be visualised graphically. The characteristics of the study cohort will be described at baseline. For objective 1, this will be done for overall diclofenac prescribing rates, diclofenac initiation rates and diclofenac discontinuation rates for any clinical indication and for individual clinical indications. For objective 2 this will be done for overall diclofenac prescribing rates in patients with a history of the following contraindications: congestive cardiac failure, ischaemic heart disease, peripheral arterial disease and cerebrovascular disease. This will also be done for overall diclofenac prescribing rates in patients with the following risk factors: hypertension; hyperlipidaemia; smoking status. For objective 3, this will be done for people initiating drug classes listed in section 3.3 following discontinuation of diclofenac.

The effect of the intervention for each country will be represented either by a step function, or by a continuous linear function representing gradual implementation (interrupted time series analysis). This choice, and whether it is necessary to model any trends prior to the intervention time point, will be decided on visual inspection of the data.[10] The analysis will be done by data source initially, and only pooled if the statistical models do not differ significantly between data sources.

5.9.3 Date of the regulatory intervention

For interrupted time series regression analysis, the date of the regulatory intervention will be pre-specified as 28 June 2013. However, the effects of the regulatory intervention may not occur immediately and may also be related to the final legally binding decision throughout the EU on 25 September 2013, which we will use as the date of the intervention as a sensitivity analysis.[1] Furthermore, we will evaluate whether any impact occurred in relation to the start of the referral (October 2012) on baseline trends. Even if prescribing patterns were in steady state before the intervention, and eventually reach a different steady state after it, the rates of transition between them may differ between countries. If there is no single measure of the effect of intervention on each outcome, but modelling the pattern of change over time is required we will used Joinpoint regression analysis.

5.9.4 Autocorrelation

It is sometimes necessary to take account of autocorrelations in time series data. However, Wagner *et al*[10] found no autocorrelation in their prescribing data. We have done some exploratory analysis of prescribing rates in CPRD and we also found none. We anticipate being able to use regression models that assume independent errors, but we will check that assumption using the Durbin Watson statistic.

5.10 LIMITATIONS

We acknowledge the limitations of each data source and the limitation of the missing data such as incomplete data for smoking status in the CPRD, Scottish and PHARMO databases and we will highlight these limitations in the report. Time to implementation of the regulatory intervention may significantly vary between data sources. If such an effect is observed following visual inspection of the data, Joinpoint regression analysis will be considered instead of interrupted time series regression analysis.[11] Another limitation of the study will be missing exposure available from over-the-counter diclofenac-containing products. Furthermore, limitations in relation to other events since the referral procedure start date (October 2012) and the PRAC Recommendation (June 2013) may have impacted on prescribing/utilisation trends (such as media reports). Updating time dependent variables at the start of each quarterly interval may result in some misclassification early in a disease, although this is not thought likely to impact on the results.

5.11 DATA PROTECTION CONSTRAINTS

For Scotland, Denmark and PHARMA databases governance requirements may mean that data with fewer than 5 patients in a time period may not be made available publicly, or even to the study statistician. The need to aggregate data further, or to redact it, will be reviewed when the extent of the problem is known.

6 WORK PLAN/QUALITY ASSURANCE PLAN

The study will be under the control of a Steering Committee who will have overall responsibility for the conduct of the study. To ensure a consistent approach is adopted across all databases, the analysis will be performed by the same principal statistician who will be supported by the working-groups who will provide aggregate data for each time series.

6.1 STEERING GROUP

The study steering group will consist of one or more representatives from each of the main data sources. The membership of this group is detailed in Appendix 4.

6.2 ADVISORY GROUP

To help with analytical issues relating to regional prescribing variation, an advisory group will be convened consisting of clinical experts familiar with NSAID prescribing practices from each country. The membership of this group will be fully detailed in the study protocol.

6.3 QUALITY ASSURANCE

The steering committee will be responsible for the overall conduct of the study. An overarching Quality Assurance plan will be developed and submitted to the agency with the draft protocol. Quality control of statistical output will be done by independent code review. The Steering Committee will apply for the "ENCePP Study Seal" demonstrating adherence to the ENCePP Code of Conduct

6.4 INFORMATION GOVERNANCE

This study will be conducted according to best practice ethical and information governance frameworks. We will adhere to the governance and legal requirements that apply to each country and database used.

7 STUDY REPORT

The final report will provide a background review to the study, full methodologies used in the study, result interpretation and discussion, and details of conduct/management of the study. Full details of all statistical outputs will be given as appendices.

8 TIMETABLE

The proposed research is planned to complete within 18 months on the following time scale.

Months	**Oct-17 to Jan-18**	**Feb-18 to Apr-18**	**May-18 to Jul-18**	**Aug-18 to Oct-18**	**Nov-18 to Jan-19**	**Feb-19 to Apr-19**
Development of the study protocol						
Protocol agreed and approved Data assembled						
Data analysis (General approach)						
Modelling of time series data						
Interim analysis/report						
Drafting final report and publication						
Manuscript ready for submission						
Monthly research committee meetings						

9 REFERENCES

1. New safety advice for diclofenac - New measures aim to minimise cardiovascular risks. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Diclofenac-containing_medicinal_products/European_Commission_final_decision/WC500155819.pdf.(Accessed on 30 May 2017)
2. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013 Aug 31;382(9894):769-79. doi: 10.1016/S0140-6736(13)60900-9. Epub 2013 May 30.
3. Krum H, Swergold G, Gammaitoni A, et al. Blood pressure and cardiovascular outcomes in patients taking nonsteroidal antiinflammatory drugs. Cardiovasc Ther. 2012 Dec;30(6):342-50. doi: 10.1111/j.1755-5922.2011.00283.x. Epub 2011 May 25.
4. Alvarez-Madrazo S, McTaggart S, Nangle C, et al. Data Resource Profile: The Scottish National Prescribing Information System (PIS). Int J Epidemiol. 2016 Jun;45(3):714-715f. doi: 10.1093/ije/dyw060. Epub 2016 May 10. No abstract available.
5. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a Tool in Epidemiology. *Eur J Epidemiol* 2014;29(8):541-9. doi: 10.1007/s10654-014-9930-3.
6. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: A Review of Content, Data Quality, and Research Potential. *Clin Epidemiol* 2015;7:449-90. doi: 10.2147/CLEP.S91125.
7. Pottegård A, Schmidt SA, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2016 Oct 27. DOI: 10.1093/ije/dyw213
8. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827-36.
9. Penning-van Beest FJ1, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. Eur Heart J 2007; 28(2): 154–159. DOI: 10.1093/eurheartj/ehl391.
10. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299-309.
11. Joinpoint Trend Analysis Software. https://surveillance.cancer.gov/joinpoint/ (Accessed on 30 May 2017)

10 APPENDICES.

Appendix 1: Clinical indications (code list to be finalised in the data extraction plan)

We will use the following codes to define the following licenced indications for diclofenac use:

1. *Pain and inflammation in musculoskeletal disorders, Acute gout (and other crystal arthropathies):*

    - Read codes: N02%
    - ICD10 codes: M10%, M11%
    - ICPC codes: T95 – gout.

2. *Pain and inflammation in rheumatic disease, including juvenile idiopathic arthritis*

Osteoarthritis

- Read codes: N05%, N06%
- ICD10 codes: M15%, M16%, M17%, M18%, M19%
- ICPC codes: L84 - arthrosis

Inflammatory arthropathies

- Read codes: N04%
- ICD10 codes: M05%, M06%, M07%, M08%, M09%
- ICPC codes: L88 - rheumatoid arthritis

ICD10 = international classification of disease version 10 (Scotland/Denmark). ICPC = international classification of primary care codes (Netherlands). % is used to denote a wildcard meaning all codes below this level in the hierarchy are included.

Appendix 2: Codes used to determine alternative medicines prescribed in patients where diclofenac has previously been prescribed (code list to be finalised in the data extraction plan)

We will use the following codes to define the following alternative medicines:

1. *Other systemic NSAIDs*
    - BNF codes: 10.01.01
    - ATC codes: M01A%
2. *Topical NSAIDs*
    - BNF codes: 10.03.02
    - ATC codes: M02AA
3. *Paracetamol*
    - BNF codes: 04.07.01
    - ATC codes: N02BE01
4. *Opioids*
    - BNF codes: 04.07.02
    - ATC codes: N02A
5. *Other chronic pain medication*
    - BNF codes: 04.08.01 (gabapentin, pregabalin), 07.04.02 (duloxetine), 04.03.01 (amitriptyline)
    - ATC codes: N03AX12 (gabapentin), N03AX16 (pregabalin), N06AX21 (duloxetine), N06AA09 (amitriptyline)

Appendix 3: Contraindicated and high risk groups (code list to be finalised in the data extraction plan)

We will use the following codes to define the following contraindicated and high risk groups:

1. *Congestive cardiac failure*

   Read codes: 14A6.00, 14AM.00, G58%

   ICD10 codes: I50%, I11.0, I13.0

   ICPC codes: K77 – decompensation cordis

2. *Ischaemic heart disease*

   Read codes: 14A3.00, 14A4.00, 14AZ.00, 14AL.00, G3.%, G30% to G34%, G35%, G38%,

   ICD10 codes: I20%, I21%, I22%, I23%, I24%, I25%

   ICPC codes: K76 – ischaemic heart disease, K75 acute myocardial infarction

   Prescribing: any nitrate prescribing (drug lists to be developed by data source according to local practice)

3. *Peripheral arterial disease*

   Read codes: 14NB.00, G7.%, G70% to G75%, G78%, G79%, K138z00

   ICD10 codes: I70%, I71%, I72%, I73.8, I73.9, I74 or I73.x, I70.2, I79.2 9

   ICPC codes: K91 atherosclerose, K99.01 aortic aneurysm, K92 other peripheral arterial diseases

4. *Cerebrovascular disease*

   Read codes: G6.%, G60% to G68%, G6W%, G6X%, G6y%, G6z%

   ICD10 codes: I60% to I69%

   ICPC codes: T90 CVA

ICD10 = international classification of disease version 10 (Scotland/Denmark). ICPC = international classification of primary care codes (Netherlands). % is used to denote a wildcard meaning all codes below this level in the hierarchy are included.

5. *Hypertension*

   Read codes: G20% to G23%

   ICD10 codes: I10% to I13%

   ICPC codes: K86, K87 – hypertension

   Prescribing: any hypertension prescribing (drug lists to be developed by data source according to local practice)

6. *Hyperlipidaemia*

   Read codes: 44P3.00, ZC2CJ00, C32%

   ICD10 codes: E78%

   ICPC codes: T93 – hyperlipidaemia

   Prescribing: any use of lipid regulating drugs (drug lists to be developed by data source according to local practice)

7. *Diabetes*

   Read codes: C10%

   ICD10 codes: E11%

   ICPC codes for diabetes: T90 – diabetes mellitus

   Prescribing: any use of diabetes medication, if possible excluding metformin used for polycystic ovary syndrome (drug lists to be developed by data source according to local practice)

ICD10 = international classification of disease version 10 (Scotland/Denmark). ICPC = international classification of primary care codes (Netherlands). % is used to denote a wildcard meaning all codes below this level in the hierarchy are included.

Appendix 4: Steering Group Members

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