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Requena, G; Logie, J; Martin, E; Boudiaf, N; Gonzalez Gonzalez, R; Huerta, C; Alvarez, A; Webb, D; Bate, A; Garca Rodriguez, LA; Reynolds, R; Schlienger, R; Gardarsdottir, H; de Groot, M; Klungel, OH; de Abajo, F; Douglas, IJ (2015) Do case-only designs yield consistent results across design and different databases? A case study of hip fractures and benzodiazepines. *Pharmacoepidemiology and drug safety*. ISSN 1053-8569 DOI: <https://doi.org/10.1002/pds.3822>

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DOI: [10.1002/pds.3822](https://doi.org/10.1002/pds.3822)

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## DO CASE-ONLY DESIGNS YIELD CONSISTENT RESULTS ACROSS DESIGN AND DIFFERENT DATABASES? A CASE STUDY OF HIP FRACTURES AND BENZODIAZEPINES .

Journal:	<i>Pharmacoepidemiology and Drug Safety</i>
Manuscript ID:	PDS-14-0399.R2
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	27-May-2015
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Keywords:	Case crossover, Self-controlled case series, benzodiazepines, hip fractures, electronic healthcare records database
Abstract:	<p>Background: The case crossover (CXO) and self-controlled case series (SCCS) designs are increasingly used in pharmacoepidemiology. In both, relative risk estimates are obtained within persons, implicitly controlling for time-fixed confounding variables.</p> <p>Objectives: To examine the consistency of relative risk estimates of hip/femur fractures (HFF) associated with the use of benzodiazepines</p>

(BZD) across case-only designs in two databases (DBs), when a common protocol was applied.

Methods: CXO and SCCS studies were conducted in BIFAP (Spain) and CPRD (UK). Exposure to BZD was divided into non-use, current, recent and past use. For CXO, odds ratios (OR; 95%CI) of current use vs. non-use/past were estimated using conditional logistic regression adjusted for co-medications (AOR). For the SCCS, conditional Poisson regression was used to estimate incidence rate ratios (IRR; 95%CI) of current use vs. non/past-use, adjusted for age. To investigate possible event-exposure dependence the relative risk in the 30 days prior to first BZD exposure was also evaluated.

Results: In the CXO current use of BZD was associated with an increased risk of HFF in both DBs, AORBIFAP=1.47 (1.29-1.67) and AORCPRD=1.55 (1.41-1.70). In the SCCS, IRRs for current exposure was 0.79 (0.72-0.86) in BIFAP and 1.21 (1.13-1.30) in CPRD. However, when we considered separately the 30 day pre-exposure period, the IRR for current period was 1.43 (1.31-1.57) in BIFAP and 1.37 (1.27-1.47) in CPRD.

Conclusions: CXO designs yielded consistent results across DBs, while initial SCCS analyses did not. Accounting for event-exposure dependence, estimates derived from SCCS were more consistent across DBs and designs.

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4 **DIFFERENT DATABASES? A CASE STUDY OF HIP FRACTURES AND**  
5 **BENZODIAZEPINES**  
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8 Running head: A comparison across case-only designs and databases.  
9

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54 **Key words:** Case crossover (CXO); Self-controlled case series (SCCS);  
55 Benzodiazepines; hip fractures; electronic healthcare records databases (DBs).  
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3 **Key points:** 1- Case-only designs may offer better control for time invariant  
4 confounding factors than traditional designs and may be a useful choice when intrinsic  
5 factors may represent relevant confounding.  
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8 2- Care is needed to ensure the underlying assumptions of these designs are met and to  
9 interpret the results obtained as they may not always generalise to patients receiving  
10 continuous treatment with the medication being assessed.  
11

12 3- In the SCCS design, it is important to explore the potential event-exposure  
13 dependence as even temporary effects can have a large impact on results.  
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15 4- This research has shown that performing multi-site studies, using a common protocol  
16 provides useful comparisons across countries and across designs.  
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21 **Specific author contribution:**

22 All authors contributed to the study conception and design. The corresponding authors  
23 responsible per DB performed data extraction and raw data analysis. GR, JL and IJD  
24 wrote the first draft and all authors contributed with critical comments to the final  
25 version.  
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27

28  
29 **Financial support:**

30 The PROTECT project has received support from the Innovative Medicines Initiative  
31 Joint Undertaking (IMI JU) ([www.imi.europa.eu](http://www.imi.europa.eu)) under *Grant Agreement* n° 115004,  
32 resources of which are composed of financial contribution from the European Union's  
33 Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in-kind  
34 contribution. As a special form of the IMI JU grant, Utrecht University and University  
35 of Alcalá received a direct financial contribution from Pfizer and Astra-Zeneca,  
36 respectively. JL, NB, DW, AB, RS, and RR belong to EFPIA (European Federation of  
37 Pharmaceutical Industries and Association) member companies in the IMI JU and costs  
38 related to their part in the research were carried by the respective company as in-kind  
39 contribution under the IMI JU scheme. The views expressed are those of the authors  
40 only and not of their respective institution or company. IJD is funded by a Medical  
41 Research Council Methodology Fellowship.  
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51  
52 **Potential competing interests:**

53 OK and MdG have received unrestricted funding for pharmacoepidemiological research  
54 from the Dutch private-public funded Top Institute Pharma.  
55

56 JL, DW and NB are employees and stockholders of GlaxoSmithKline.  
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3 RS is a Novartis employee and owns Novartis shares.

4 AB and RR are employees and stockholders of Pfizer, Inc.

5  
6 IJD consults for and holds stock in GSK, and consults for Gilead.  
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9  
10 **Acknowledgements:**

11 The research leading to these results was conducted as part of the PROTECT  
12 consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a  
13 European ConsorTium, [www.imi-protect.eu](http://www.imi-protect.eu)) which is a public-private partnership  
14 coordinated by the European Medicines Agency. The paper is on behalf of WP2  
15 (members can be found at introduction of the special issue).  
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18 The authors would like to thank the excellent collaboration of physicians in the  
19 participating countries, whose contribution in recording their professional practice with  
20 high quality standards makes possible the availability of DBs used in this research.  
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25 **Word Count main text: 3,334**  
26

27 An abstract of this paper has been submitted to participate as a poster in the **ICPE 2014**,  
28 30th International Conference on Pharmacoepidemiology & Therapeutic Risk  
29 Management, with the abstract number #433.  
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**ABSTRACT**

**Background:** The case crossover (CXO) and self-controlled case series (SCCS) designs are increasingly used in pharmacoepidemiology. In both, relative risk estimates are obtained within persons, implicitly controlling for time-fixed confounding variables.

**Objectives:** To examine the consistency of relative risk estimates of hip/femur fractures (HFF) associated with the use of benzodiazepines (BZD) across case-only designs in two databases (DBs), when a common protocol was applied.

**Methods:** CXO and SCCS studies were conducted in BIFAP (Spain) and CPRD (UK). Exposure to BZD was divided into non-use, current, recent and past use. For CXO, odds ratios (OR; 95%CI) of current use vs. non-use/past were estimated using conditional logistic regression adjusted for co-medications (AOR). For the SCCS, conditional Poisson regression was used to estimate incidence rate ratios (IRR; 95%CI) of current use vs. non/past-use, adjusted for age. To investigate possible event-exposure dependence the relative risk in the 30 days prior to first BZD exposure was also evaluated.

**Results:** In the CXO current use of BZD was associated with an increased risk of HFF in both DBs,  $AOR_{BIFAP}=1.47$  (1.29-1.67) and  $AOR_{CPRD}=1.55$  (1.41-1.70). In the SCCS, IRRs for current exposure was 0.79 (0.72-0.86) in BIFAP and 1.21 (1.13-1.30) in CPRD. However, when we considered separately the 30 day pre-exposure period, the IRR for current period was 1.43 (1.31-1.57) in BIFAP and 1.37 (1.27-1.47) in CPRD.

**Conclusions:** CXO designs yielded consistent results across DBs, while initial SCCS analyses did not. Accounting for event-exposure dependence, estimates derived from SCCS were more consistent across DBs and designs.

Word count: 248

## INTRODUCTION

Case only designs overcome some key confounding issues such as lack of information on potential confounders, and difficulties in selecting appropriate controls in numerous settings <sup>1</sup>. One common characteristic of those designs is that comparisons are within-person not between-persons, thereby controlling implicitly for all intrinsic factors, both measured and unmeasured, that remain constant over the study period. For these reasons they are increasingly being used in pharmacoepidemiology <sup>2</sup>.

The case crossover (CXO) method was developed by Maclure (1991), to investigate the risk of transient and immediate acute events <sup>3</sup>. The particularity is that “controls” come from the person-time of the case. It uses the difference in exposure rates just before the event (the ‘case moment’) with those at other times (‘controls moments’) to estimate an odds ratio (OR) of the outcome associated with exposure. It depends on strong assumptions, being suitable for transient exposures with short term effects<sup>4</sup>. Hence, the intermittency of drug use and the length of the exposure time window may have an impact on the estimates obtained <sup>2</sup>. Also, as a conditional logistic regression model is employed with more than one control moment, distribution of exposures must be exchangeable between those periods to emulate a case-control design where the order of controls is irrelevant <sup>5</sup>.

The self-controlled case series (SCCS) method was developed by Farrington (1995) to study the association between vaccination and adverse events <sup>6</sup>. The SCCS follows the cohort design approach, it is derived from a Poisson distribution model by conditioning on an individual’s total number of events and their exposure history <sup>7</sup>.

The SCCS is based on several assumptions; one is that the occurrence of the event of interest does not influence the chance of subsequent exposure. However, in situations where the event could temporarily increase or decrease the likelihood of exposure, a valid approach is to separately categorise a short period of time before exposure, thereby removing this time from the reference category (baseline or period of no exposure) to avoid a biased event rate in that period.

Since the designs share some features but follow a different approach, we assessed whether they reached similar results across electronic healthcare records databases (DBs) from the United Kingdom (UK) and Spain following the same protocol and



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3 methodology. As a case study we used the well-established association<sup>8,9</sup> of  
4 benzodiazepines and related drugs (BZD) with hip/femur fractures (HFF). BZD are  
5 often used intermittently and with these case-only designs some confounding such as  
6 frailty could be addressed.  
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10 The present research was undertaken within the frame of the  
11 Pharmacoepidemiological Research on Outcomes of Therapeutics by a European  
12 Consortium (IMI-PROTECT) project (<http://www.imi-protect.eu/>).  
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## 15 16 17 **PATIENTS AND METHODS**

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19 The study was performed in two primary care DBs: The UK Clinical Practice  
20 Research Datalink (CPRD GOLD)<sup>10</sup>, and “Base de datos para la Investigación  
21 Farmacoepidemiológica en Atención Primaria” (BIFAP) from Spain. These DBs have  
22 been described in detail elsewhere<sup>11</sup>. The protocol was registered in The European  
23 Network of Centres for Pharmacoepidemiology and Pharmacovigilance, ENCePP<sup>12</sup>. A  
24 blinding procedure was maintained until results were made available to the coordinating  
25 centre at Utrecht University, the Netherlands.  
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### 31 32 **Study population**

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34 The study period was considered from the 1<sup>st</sup> January 2001 until 31<sup>st</sup> December  
35 2009. All data were used when the practices were considered “Up to (research)  
36 Standard” (a marker of data quality). Patients who had at least one year of registration  
37 with the general practitioner (GP), were  $\geq 18$  years old, and were 12 months free of HFF  
38 were included in the study population. All patients were required to have a recorded  
39 diagnosis of HFF during the study period, i.e. they were all “cases”. For the SCCS,  
40 patients were required to have 6 months free of BZD prescriptions before entering the  
41 study to restrict the population to new users. This criterion was not applied for the CXO  
42 to ensure all case or control moments had the opportunity to be exposed to BZD.  
43 Patients could enter at any time they fulfilled the criteria above. The start date was the  
44 date patients met the cited criteria.  
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### 53 54 **Case definition**

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57 HFF was searched in the BIFAP database using the International Classification of  
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3 Primary Care: ICPC-2, code L75 and in CPRD using READ codes (Table S1 online). In  
4 BIFAP, cases were identified through free-text (in addition to codes). For that reason, a  
5 review of all cases was carried out for validation. As a result, similar to the companion  
6 Cohort/NCC paper<sup>13</sup>, 30% of cases were excluded (of them, about 15% due to high-  
7 energy trauma, 60% due to other fractures (i.e. pelvis), and the remaining patients did  
8 not have a clear date of the event). Such a revision was not feasible in the CPRD, but  
9 previous validation confirmed 91% of recorded hip fractures in the CPRD<sup>14</sup>. In patients  
10 with a history of past HFF, a minimum of 12 months must have elapsed between the  
11 current episode and any previous fracture to ensure these represented separate events.  
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## 22 **Exposure definition**

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24 BZD was the exposure of interest, comprising all those classified as anxiolytics,  
25 hypnotics and related drugs in the Anatomical Therapeutic Chemical (ATC)  
26 classification<sup>15</sup>. (Supplementary Table S2 online). Related drugs (Z-drugs and  
27 clomethiazole) were included in this research because their therapeutic actions are  
28 similar to benzodiazepines<sup>16</sup>.  
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34 Duration of each prescription was estimated based on the prescribed amount and  
35 daily dose. The expected duration of use was calculated following the methods of  
36 Gardarsdottir et al<sup>17</sup>. When a gap of more than 30 days occurred between the theoretical  
37 end date of a prescription and the date of the subsequent prescription, exposure was  
38 considered to be discontinuous, and a new treatment episode was considered.  
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43 The person-time of each patient was divided according to their exposure into periods  
44 of current, recent, past and non-use. Thus, current use was the period from the start of a  
45 BZD prescription until 30 days after the estimated end date of the supply; recent use  
46 was the period up to 60 days after current use; past use was the period after recent use  
47 until the patient became exposed again or the end of follow-up; non-use was the period  
48 between the start date and the first BZD prescription within the study period. Combined  
49 non-use and past use was considered the reference category or baseline (Figure 1). For  
50 the SCCS, current use was further divided into five risk time windows: 1-30, 31-60, 61-  
51 182, 183-365 and >365 days. BZD are thought to increase the risk of fractures during  
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3 the early stages of treatment<sup>18,19</sup> and this was taken into account when defining exposure  
4 time windows.  
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7 For the CXO, each case serves as its own control, and up to four control moments  
8 were defined at 91, 182, 273 and 365 days prior to the HFF (case moment). This  
9 method assumes that the baseline risk for an exposure is constant, and this assumption  
10 was tested using up to four control periods per case, improving the precision of the  
11 effect size, and the efficiency by using the whole year prior to the event<sup>20</sup>.  
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16 For each patient, exposure at the case moment was compared to exposure at control  
17 moments. In addition for this design, the current use period was further categorized as  
18 single use of anxiolytics, single use of hypnotics, and use of both.  
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### 22 **Potential confounders**

23 These studies are part of a common protocol where four analytical study designs were  
24 performed to investigate the same study question  
25 (<http://www.encepp.eu/encepp/viewResource.htm?id=6179>).  
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32 In the CXO, all medications mentioned in the protocol (See Table S3 online) were  
33 considered as potential confounders. Indicator terms for medication use were added to  
34 the model denoting the absence or presence of prescriptions of each separate type  
35 of medication listed in Table S3, within the 91 days prior to the case or control  
36 moments.  
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41 In the SCCS, age was considered as the most important potential confounder, given  
42 its strong association with fracture risk<sup>21</sup> and given that many relevant unmeasured  
43 factors are likely to be age-related (e.g. frailty or increase in severity of underlying  
44 diseases) as well as related to BZD pattern of use.  
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### 49 **Analysis**

50 Analyses in BIFAP were performed using Stata®-11, in CPRD analyses were  
51 performed using SAS v9.2 for the CXO and Stata®-10 for the SCCS.  
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56 In the CXO, conditional logistic regression was used to estimate the relative risk in  
57 terms of ORs with corresponding 95% confidence intervals (CI).  
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3 In the SCCS, conditional Poisson regression was used to estimate the relative risk in  
4 terms of incidence rate ratios (IRRs) with corresponding 95% CI<sup>22</sup>.  
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7 To examine potential event-exposure dependence, a pre-exposure time risk window  
8 was created in the SCCS with a length of 30 days, allowing us to examine whether an  
9 incident HFF has a short term impact on the likelihood of being prescribed a BZD. IRR  
10 were estimated excluding this pre-exposure time of 30 days from the reference category  
11 in a sensitivity analysis.  
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## 15 16 17 **RESULTS**

### 18 Case Crossover

#### 19 *Characteristics of study populations (BIFAP and CPRD)*

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21 In BIFAP, 5,412 cases were included, with a similar mean age of 78 ( $\pm 13$ ) years old.  
22 From these, 85% contributed four control moments (Table 1). In CPRD, a total of  
23 12,853 cases of HFF were included as the study population, with a mean age ( $\pm$ SD) of  
24 79 ( $\pm 13$ ) years old. From these, 88% were also registered in the DB during the four  
25 control moments. Distribution by sex was similar in both DBs, 78% females and 22%  
26 males. The characteristics of patients are described in Table S4 online.  
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#### 34 *Effect of BZD (BIFAP and CPRD)*

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36 Crude ORs (95%CI) and adjusted OR (AORs) (95%CI) for current use of BZD,  
37 compared to past/non-use, were similar between DBs: OR=1.70 (1.50-1.92), AOR=1.47  
38 (1.29-1.67) in BIFAP and OR=1.75 (1.60-1.92), AOR=1.55 (1.41-1.70) in CPRD  
39 (Figure 2).  
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#### 45 *Effect of BZD treatment duration in CPRD*

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47 In CPRD, although the highest relative risk was observed within the first 30 days of  
48 treatment AOR (95%CI): 1.70 (1.49-1.94), a model accounting for duration class did  
49 not provide a significantly better fit to the data than one considering presence/absence  
50 of BZD exposure alone (chi-square for comparison of  $-2\log L$  scores = 6.82, DF = 4, p  
51 = 0.15) (Figure 3).  
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### 57 Self-Controlled Case Series

### *Characteristics of study populations (BIFAP and CPRD)*

In CPRD, a total of 8,333 cases were included as the study population and a total of 4,450 cases were included in BIFAP. In both populations the age and gender distribution was similar; 77% and 74% were females in BIFAP and CPRD respectively. The mean age at first exposure to BZD was about 76 years old in both DBs. The percentage of HFF occurring during the exposure to BZD (current use) was higher in BIFAP (35%) than in CPRD (22%), and the median duration of the observation period was shorter in BIFAP (5.4 years) than in CPRD (7.0 years). Of 8,333 patients exposed to BZD in CPRD, 4,790 had only a single continuous period of BZD exposure compared to 3,543 patients (42.52%) who had intermittent BZD use. In the same way, of 4,450 patients exposed to BZD in BIFAP, 1,782 had only a single continuous period of BZD exposure compared to 2,668 (59.96%) who had intermittent BZD use.

### *Effect of BZD and related drugs*

Adjusted IRR of HFF associated with current use was 1.21 (1.13-1.30) in CPRD and 0.79 (0.72-0.86) in BIFAP in analyses ignoring the potential for event-exposure dependence. In CPRD, an apparent decreasing trend of risk with duration of treatment was observed, ranging from 1.42 (1.27-1.59) in the first 30 days of use to 0.89 (0.79-1.02) with >365 days of use. In BIFAP, no increased risk was observed in any time window category (Table 2).

### *Sensitivity analysis of event-exposure dependence*

When a 30 day pre-exposure window was removed from the reference period, an increased risk was observed across all exposure period time windows. The highest risk was exhibited by the pre-exposure time window, with 2.52 (95%CI: 2.30-2.76) and 6.47 (95%CI: 5.91-7.09) adjusted for age, in CPRD and BIFAP, respectively. Excluding this pre-exposure time from the reference category we observed in BIFAP a marked change in the magnitude of the estimates, over all exposure time windows, reaching an IRR of 1.43 (1.31-1.57) when current use was aggregated in just one category. Such increment was less for CPRD varying from 1.21 (1.13-1.30) to 1.37 (1.27-1.47) in the current use category (Table 3).

## DISCUSSION

Under PROTECT's framework of Pharmacoepidemiology studies, four analytical designs were performed in different databases focusing on the methodological aspects of the studies rather than the clinical consequences of the association under investigation. Two case-only designs, studying the association of BZD with HFF are presented here. The results of the cohort and nested case-control (NCC) studies for the same association are presented elsewhere<sup>13</sup>.

### *CXO study*

Crude and AORs were similar between databases. Other CXO studies showed similar associations. Neutel et al<sup>23</sup>, for example, found a crude OR = 1.7, 95%CI: 1.0-2.9, for exposure to BZD and Berry et al<sup>24</sup> found an AOR = 1.66, 95%CI: 1.45-1.90 associated with the use of non-BZD hypnotics.

Concerning the *effect of BZD subgroup*, in both DBs the highest risk was observed in patients taking both anxiolytics and hypnotics, similar to the results seen with other study designs evaluated in PROTECT<sup>13</sup>. As falls and fractures are dose-related adverse effects<sup>25</sup>, the use of several drugs could be seen as equivalent to the use of a higher dose. Alternatively, this could partly be related to the higher severity of the underlying conditions of these patients.

Regarding the *effect of BZD treatment duration* in CPRD, although the highest relative risk was observed within the first 30 days of treatment AOR (95%CI): 1.70 (1.49-1.94), a duration effect was not supported by formal test ( $p=0.15$ ). There is a lack of published articles exploring this short-term effect of BZD and related drugs with this design. This method assumes immediate and transient effect as well as intermittent exposures and the power to detect the effect of continuous treatment may be limited. Possible explanations for increasing or decreasing the risk with duration of treatment have been discussed previously<sup>13</sup>.

In BIFAP, it was not possible to examine duration of use in this design because data available before the study period were insufficient for assessing all duration categories.

### *SCCS study*

An increased risk of HFF with the use of BZD was observed in CPRD but not in any exposure category in initial analyses after adjusting for age in BIFAP (Table 2).

However, within these analyses, we found evidence of a strong but temporary dependence of event and exposure implying that some patients who sustained a HFF were prescribed a BZD shortly after the event. This dependence violates one of the key assumptions of this design. Separating a 30 day period from the reference category, the results in the SCCS were similar to the CXO in both BIFAP and CPRD, again suggesting an increased fracture risk associated with exposure to BZD in all current use windows.

Gibson et al <sup>22</sup> also used a pre-exposure time to assess the risk of motor vehicle crashes with BZD, and found elevated risks (IRR= 1.94, 99% CI: 1.62, 2.32). A similar situation was observed by Lai C et al <sup>14</sup> studying the risk of HFF associated with alpha blockers using a SCCS design.

### *Comparison across all designs*

Both traditional (cohort and NCC) and case only designs suggested an increased risk of HFF associated with current use of BZD. However, designs differed in the magnitude of risk with traditional designs showing slightly lower relative risks (RR) than case-only designs. Differences observed between designs might be due to the fact that chronic users of BZD with no unexposed observation time are excluded from the estimated RR in the case only designs, but can contribute in cohort and NCC analyses. Results must be interpreted in the light of these differences and in some instances, case only results may be more accurately generalised to intermittent users. If chronic users of BZD had a lower risk than short term users, explained by a better adaptation of regular users to those drugs or by the consequence of 'healthy user effect'<sup>26</sup>, traditional designs would be expected to yield lower RR estimates than case-only designs. Conversely, traditional designs estimate between-person RR, while case-only estimate within-person RR<sup>27,28</sup>, which may not be necessarily of the same magnitude due to unmeasured factors difficult to adjust for such as severity of underlying diseases, or frailty. Such factors may increase the risk of fall and fractures and may make physicians reluctant to prescribe



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3 BZD (e.g. confounding by contraindication). This confounding would lead to an  
4 underestimate of the relative risk of HFF associated with BZD use. In case-only  
5 designs, time invariant confounding factors are implicitly controlled for by design,  
6 although a confounding by transient changes in other factors cannot be excluded.  
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10 The fact that the cohort/NCC analyses were restricted to BZD users with a reference  
11 category of past-use, and therefore, all patients were exposed at least once to the drug of  
12 interest, made the comparison between cohort members more similar than if an external  
13 cohort of non-users had been used. In contrast, a reference category of non-use was  
14 appropriate for the case-only analyses, as differences between persons are removed by  
15 design.  
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19 Results obtained with both case-only designs were similar, although the precision of  
20 the estimates was higher in the SCCS than in the CXO which may be consider as  
21 potential advantage of the former.  
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25 The experience of comparing different designs using the same source population is  
26 limited. The study of Madigan et al<sup>29</sup>, part of the Observational Medical Outcomes  
27 Partnership (OMOP) project, studied this drug-event pair employing a SCCS and a  
28 cohort design within the same data source, and compared the results across ten DBs.  
29 Seven out of ten DBs found no increased risk of HFF associated with BZD use, when a  
30 SCCS was employed. However, this study was not specific to BZD-HFF, and explored  
31 53 drug-event pairs under a surveillance perspective rather than specifically addressing  
32 this pair in a formal hypothesis testing study with a pair specific protocol.  
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36 There are some publications comparing designs yielding different results, although  
37 studying different associations<sup>30,31</sup>. In most articles, relative risk estimates with case  
38 only designs were lower than those obtained with cohort or NCC designs, with authors  
39 generally concluding that the higher estimates obtained using these designs may be due  
40 to between-person confounding.  
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### 43 *Strengths and limitations*

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45 We only had access to prescribing data, rather than the precise dates on which  
46 medication was actually taken. It is therefore possible that exposure periods are  
47 misclassified to some extent, with both exposed and unexposed periods affected to some  
48 extent.  
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3 degree. The effect of this would tend to bias results towards the null, and so it is  
4 possible that we have underestimated any real effect of treatment with BZD. A major  
5 strength of this research is the use of a common protocol allowing the use of  
6 harmonized methods and definitions across DBs, aiding the direct comparison of  
7 results.  
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12 In general, case-only designs are limited by their underlying assumptions. In this  
13 study, the assumption of independence between event and exposure in the SCCS design  
14 was not met but was subsequently corrected for by the use of a pre-exposure risk  
15 period<sup>22</sup>.  
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20 In our case only two DBs have been employed with just one drug-event association,  
21 so results might not be extrapolated to other settings and certainly not be generalised to  
22 other drug-event pairs.  
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## 25 26 CONCLUSIONS

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29 CXO designs yielded consistent results across DBs. Once we accounted for the  
30 event-exposure dependence, estimates derived from SCCS were also consistent across  
31 DBs and across designs. Case-only designs may offer better control for time invariant  
32 confounding factors than traditional designs and are a useful choice when intrinsic  
33 factors may represent relevant confounding, and when the effects of transient exposures  
34 are to be measured. Care is needed to ensure the underlying assumptions of these  
35 designs are met and to interpret the results obtained as they may not always generalise  
36 to patients receiving continuous treatment with the medication being assessed.  
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43 These studies together with the cohort and case control analyses have shown that  
44 performing multi-site studies using a common protocol provides useful comparisons  
45 across countries and across designs, contributing to a better understanding of potential  
46 differences between pharmacoepidemiological studies used to assess drug safety.  
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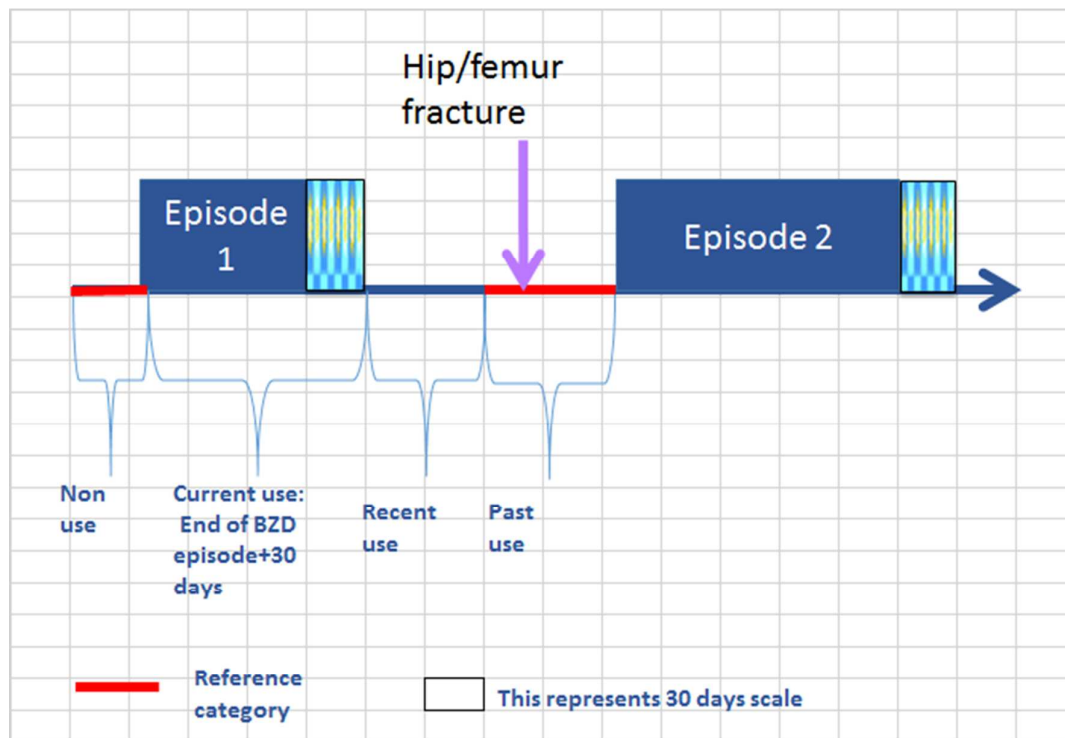


Figure 1. Structure of exposure definition. The follow-up continued beyond the date of hip/femur fracture only for the SCCS.

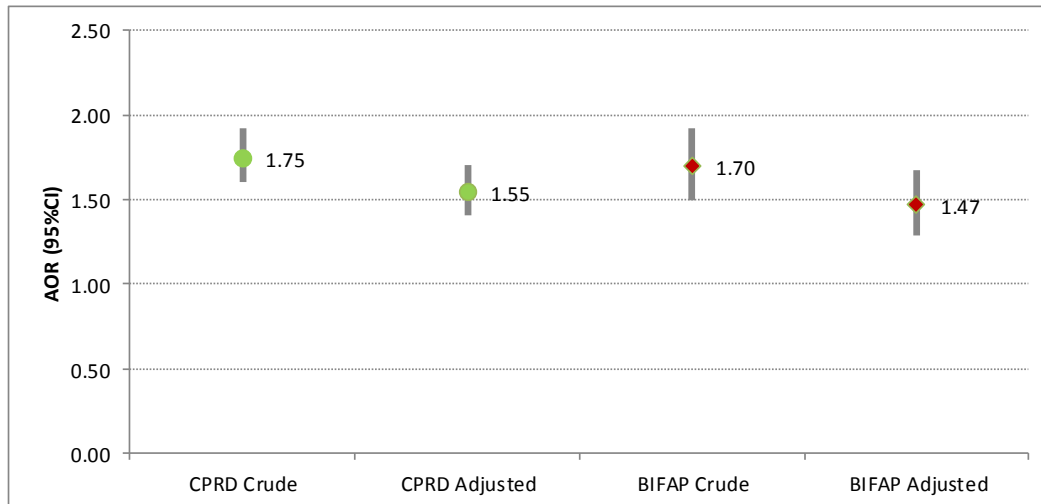
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Table 1. Number of cases and its control moments participating in case-crossover study in BIFAP and CPRD.

Control Moments(M)	Number of cases with M controls (N%)		Number of cases with at least M controls (N%)	
	CPRD	BIFAP	CPRD	BIFAP
1	530 (4.1)	267 (4.7)	12,853 (100)	5,412 (100)
2	474 (3.7)	272 (4.8)	12,323 (95.9)	5,145 (95.1)
3	492 (3.8)	274 (4.8)	11,849 (92.2)	4,873 (90.0)
4	11,357 (88.4)	4,599 (80.6)	11,357 (88.4)	4,599 (85.0)

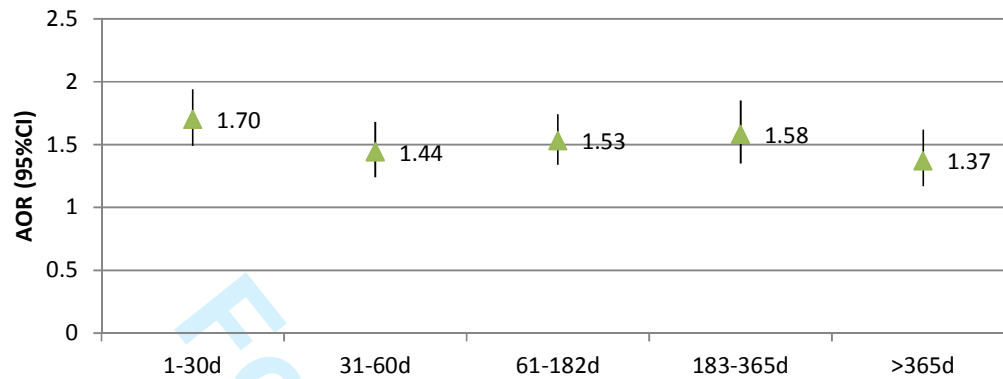
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Figure 2. Crude and co-medication adjusted risk of hip/femur fracture associated to current use of BZD. Case-crossover study.



	CPRD				BIFAP			
	Cases N=12,853		Sum of controls N=48,382		Cases N=5,412		Sum of controls N=20,029	
	N	%	N	%	N	%	N	%
Non/past use	7838	60.98	31567	65.25	2493	46.06	9928	49.57
Recent use	610	4.75	1256	2.60	367	6.78	1020	5.09
Current use	4405	34.27	15559	32.16	2552	47.15	9081	45.34

Figure 3. Co-medication adjusted risk of hip/femur fracture associated to duration of current use of BZD in CPRD. Case-crossover study.



Cases, N(%)	377 (8.84)	284 (6.66)	490 (11.49)	428 (10.03)	2,687 (62.99)
Σcontrols, N(%)	1,036 (2.14)	1,724 (3.56)	2,962 (6.12)	1,480 (3.06)	10,079 (20.83)

Table 2. Risk of hip/femur fracture associated with current use of BZD from SCCS studies in BIFAP and CPRD without adjustment for event-exposure dependence.

	BIFAP (N=4,450)								CPRD (N=8,333)							
			Model Crude			Model Adjusted by age					Model Crude			Model Adjusted by age		
	Cases	Follow up days	IRR	IC(95%)		IRR	IC(95%)		Cases	Follow up days	IRR	IC(95%)		IRR	IC(95%)	
<b>Past/Non-use</b>	2,615	5,169,915	1.00	-	-	1.00	-	-	6,060	15,769,427	1.00	-	-	1.00	-	-
<b>Recent use</b>	292	476,872	1.14	1.00	1.29	0.97	0.85	1.10	439	792,974	1.42	1.28	1.57	1.26	1.14	1.39
<b>Current use</b>	1,543	2,945,532	1.02	0.94	1.11	0.79	0.72	0.86	1,834	3,274,091	1.55	1.45	1.66	1.21	1.13	1.30
<b>1-30 days</b>	213	409,985	0.92	0.80	1.07	0.79	0.68	0.92	342	510,624	1.59	1.42	1.78	1.42	1.27	1.59
<b>31-60 days</b>	201	362,943	0.99	0.85	1.15	0.85	0.73	0.99	253	425,445	1.44	1.27	1.64	1.27	1.11	1.44
<b>61-182 days</b>	314	614,880	0.93	0.82	1.06	0.75	0.66	0.86	383	647,956	1.48	1.33	1.66	1.19	1.06	1.33
<b>183-365 days</b>	246	437,601	1.11	0.95	1.29	0.83	0.71	0.96	300	498,354	1.66	1.46	1.89	1.20	1.05	1.37
<b>&gt;365 days</b>	569	1,120,123	1.28	1.12	1.47	0.73	0.63	0.84	556	1,191,712	1.62	1.43	1.82	0.89	0.79	1.02



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Table 3. Risk of hip/femur fracture associated with current use of BZD from SCCS studies in BIFAP and CPRD including adjustment for event-exposure dependence.

	BIFAP (N=4,450)								CPRD (N=8,333)							
	Cases	Follow up days	Model Crude			Model Adjusted by age			Cases	Follow up days	Model Crude			Model Adjusted by age		
			IRR	IC(95%)		IRR	IC(95%)				IRR	IC(95%)		IRR	IC(95%)	
<b>Past/Non-use</b>	1,898	4,941,912	1.00	-	-	1.00	-	-	5,549	15,344,912	1	-	-	1	-	-
<b>Recent use</b>	172	361,218	1.37	1.16	1.60	1.21	1.03	1.42	401	712,289	1.58	1.43	1.76	1.41	1.27	1.57
<b>Current use</b>	1,543	2,945,532	1.77	1.62	1.93	1.43	1.31	1.57	1,834	3,274,091	1.75	1.63	1.87	1.37	1.27	1.47
<b>1-30 days</b>	213	409,985	1.58	1.36	1.83	1.40	1.21	1.62	342	510,624	1.79	1.60	2.00	1.59	1.42	1.78
<b>31-60 days</b>	201	362,943	1.69	1.45	1.97	1.49	1.28	1.74	253	425,445	1.62	1.43	1.85	1.42	1.25	1.62
<b>61-182 days</b>	314	614,880	1.63	1.43	1.86	1.37	1.20	1.57	383	647,956	1.68	1.50	1.89	1.35	1.20	1.51
<b>183-365 days</b>	246	437,601	1.95	1.68	2.27	1.53	1.32	1.79	300	498,354	1.88	1.65	2.14	1.36	1.19	1.55
<b>&gt;365 days</b>	569	1,120,123	2.27	1.97	2.60	1.42	1.22	1.65	556	1,191,712	1.83	1.62	2.06	1.02	0.90	1.16
<b>Pre-exposure period</b>	837	343,657	7.17	6.55	7.84	6.47	5.91	7.09	549	505,200	2.83	2.59	3.11	2.52	2.30	2.76

## CONFLICT OF INTEREST DISCLOSURE

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2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions.  Yes  NO  N/A
3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted.  Yes  NO  N/A

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**Corresponding author and Co-authors:**

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5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied.  Yes  NO  N/A

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7 6. In the past three years I have:

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- 9 • been paid as a consultant (or in a similar capacity) by a company with a vested interest in the  
10 product being studied, on issues related to the product being studied; No
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  - 12 • been paid as a consultant (or in a similar capacity by a company with a vested interest in the  
13 product being studied, on issues unrelated to the product being studied; No
  - 14
  - 15 • received research or educational support from a company with a vested interest in the product(s)  
16 being studied. No
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20 7. A company whose product is being studied has provided funding to support the work on this  
21 project. Yes

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25 If you have answered YES to any of the above questions, or if you have additional personal, commercial or  
26 academic conflicts of interest, please draft a statement to publish with the article, e.g., AB has been  
27 reimbursed by Safe Drug Ltd. for international conference attendance.

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30 *Andrew Bate is an employee and shareholder of Pfizer*

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34 8. Manuscript title (first six words are sufficient)

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36 **DO CASE-ONLY DESIGNS YIELD CONSISTENT RESULTS ACROSS DESIGN AND DIFFERENT DATABASES?**  
37 **A CASE STUDY OF HIP FRACTURES AND BENZODIAZEPINES**

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40 9. Author's full name (a separate form must be submitted for each author)

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2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a
3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. n/a

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5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

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**ARTURO ALVAREZ GUTIERREZ**

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Dave Webb

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FRANCISCO J. DE ABAJO

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9. Author's full name (a separate form must be submitted for each author)

John Logie

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luis alberto garcia rodriguez

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28 MdG received indirect funding from Top Institute Pharma (NL) www.tipharma.com. This public private  
29 partnership (funding 50% Government, 25% Academia, 25% pharmaceutical industry) paid 50% of his salary  
30 for the Mondriaan project to connect health care databases in the Netherlands. Ended in June 2013  
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Nada Boudiaf

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6. In the past three years I have:

- been paid as a consultant (or in a similar capacity) by a company with a vested interest in the product being studied, on issues related to the product being studied; No
- been paid as a consultant (or in a similar capacity by a company with a vested interest in the product being studies, on issues unrelated to the product being studied; No
- received research or educational support from a company with a vested interest in the product(s) being studied. No

7. A company whose product is being studied has provided funding to support the work on this project. Yes

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If you have answered YES to any of the above questions, or if you have additional personal, commercial or academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been reimbursed by Safe Drug Ltd. for international conference attendance.

Raymond G. Schlienger is an employee of Novartis Pharma AG

---

8. Manuscript title (first six words are sufficient)

DO CASE-ONLY DESIGNS YIELD CONSISTENT RESULTS ACROSS DESIGN AND DIFFERENT DATABASES?  
A CASE STUDY OF HIP FRACTURES AND BENZODIAZEPINES

9. Author's full name (a separate form must be submitted for each author)

Raymond G. Schlienger

10. In checking this box, I confirm I have completed this form to the best of my knowledge.

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October 2011

Table S1 online- ICPC-2 and READ Codes for hip/femur fracture (BIFAP and CPRD databases)

<b>CODES</b>	<b>HIP/FEMUR FRACTURES</b>
<b>ICPC-2</b>	
L75	Fracture: femur
<b>READ</b>	<b>HIP FRACTURES</b>
7K1L400	CLOSED REDUCTION OF FRACTURE OF HIP
S30..00	FRACTURE OF NECK OF FEMUR
S30..11	HIP FRACTURE
S300.00	CLOSED FRACTURE PROXIMAL FEMUR, TRANSCERVICAL
S300000	Cls # prox femur, intracapsular section, unspecified
S300100	CLOSED FRACTURE PROXIMAL FEMUR, TRANSEPIPHYSEAL
S300200	CLOSED FRACTURE PROXIMAL FEMUR, MIDCERVICAL SECTION
S300300	CLOSED FRACTURE PROXIMAL FEMUR, BASICERVICAL
S300311	CLOSED FRACTURE, BASE OF NECK OF FEMUR
S300400	CLOSED FRACTURE HEAD OF FEMUR
S300500	Cls # prox femur, subcapital, Garden grade unspec.
S300600	CLOSED FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE I
S300700	CLOSED FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE II
S300800	CLOSED FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE III
S300900	CLOSED FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE IV
S300A00	CLOSED FRACTURE OF FEMUR, UPPER EPIPHYSIS
S300y00	CLOSED FRACTURE PROXIMAL FEMUR, OTHER TRANSCERVICAL
S300y11	CLOSED FRACTURE OF FEMUR, SUBCAPITAL
S300z00	CLOSED FRACTURE PROXIMAL FEMUR, TRANSCERVICAL, NOS
S301.00	OPEN FRACTURE PROXIMAL FEMUR, TRANSCERVICAL
S301000	Opn # proximal femur, intracapsular section, unspecified
S301100	OPEN FRACTURE PROXIMAL FEMUR, TRANSEPIPHYSEAL
S301200	OPEN FRACTURE PROXIMAL FEMUR, MIDCERVICAL SECTION
S301300	OPEN FRACTURE PROXIMAL FEMUR, BASICERVICAL
S301311	OPEN FRACTURE BASE OF NECK OF FEMUR
S301400	OPEN FRACTURE HEAD, FEMUR
S301500	OPEN FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE UNSPEC
S301600	OPEN FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE I
S301700	OPEN FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE II
S301800	OPEN FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE III
S301900	OPEN FRACTURE PROXIMAL FEMUR, SUBCAPITAL, GARDEN GRADE IV
S301A00	OPEN FRACTURE OF FEMUR, UPPER EPIPHYSIS
S301y00	OPEN FRACTURE PROXIMAL FEMUR, OTHER TRANSCERVICAL
S301y11	OPEN FRACTURE OF FEMUR, SUBCAPITAL
S301z00	OPEN FRACTURE PROXIMAL FEMUR, TRANSCERVICAL, NOS
S302.00	CLOSED FRACTURE OF PROXIMAL FEMUR, PERTROCHANTERIC
S302000	Cls # proximal femur, trochanteric section, unspecified
S302011	CLOSED FRACTURE OF FEMUR, GREATER TROCHANTER
S302012	CLOSED FRACTURE OF FEMUR, LESSER TROCHANTER
S302100	CLOSED FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, TWO PART
S302200	CLOSED FRACTURE PROXIMAL FEMUR, SUBTROCHANTERIC
S302300	Cls # proximal femur, intertrochanteric, comminuted
S302400	CLOSED FRACTURE OF FEMUR, INTERTROCHANTERIC



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3	S302z00	Cls # of proximal femur, pertrochanteric section, NOS
4	S303.00	OPEN FRACTURE OF PROXIMAL FEMUR, PERTROCHANTERIC
5	S303011	OPEN FRACTURE OF FEMUR, GREATER TROCHANTER
6	S303012	OPEN FRACTURE OF FEMUR, LESSER TROCHANTER
7	S303100	OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, TWO PART
8	S303200	OPEN FRACTURE PROXIMAL FEMUR, SUBTROCHANTERIC
9	S303300	OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, COMMINUTED
10	S303400	OPEN FRACTURE OF FEMUR, INTERTROCHANTERIC
11	S303z00	OPEN FRACTURE OF PROXIMAL FEMUR, PERTROCHANTERIC, NOS
12	S304.00	PERTROCHANTERIC FRACTURE
13	S305.00	SUBTROCHANTERIC FRACTURE
14	S30w.00	CLOSED FRACTURE OF UNSPECIFIED PROXIMAL FEMUR
15	S30x.00	OPEN FRACTURE OF UNSPECIFIED PROXIMAL FEMUR
16	S30y.00	CLOSED FRACTURE OF NECK OF FEMUR NOS
17	S30y.11	HIP FRACTURE NOS
18	S30z.00	OPEN FRACTURE OF NECK OF FEMUR NOS
19	S4E..00	FRACTURE-DISLOCATION OR SUBLUXATION HIP
20	S4E0.00	CLOSED FRACTURE-DISLOCATION, HIP JOINT
21	S4E1.00	OPEN FRACTURE-DISLOCATION, HIP JOINT
22	S4E2.00	CLOSED FRACTURE-SUBLUXATION, HIP JOINT
23	S4E3.00	OPEN FRACTURE-SUBLUXATION, HIP JOINT
24	<b>READ</b>	<b>FEMUR FRACTURES</b>
25	7K1G200	Primary open reduction+external fixation of femoral fracture
26	7K1L500	CLOSED REDUCTION OF FRACTURE OF FEMUR
27	K7805F	REDUCTION CLOSED FRACTURE FEMUR
28	K7815F	REDUCTION OPEN FRACTURE FEMUR
29	S31..00	OTHER FRACTURE OF FEMUR
30	S310.00	CLOSED FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART
31	S310000	CLOSED FRACTURE OF FEMUR, UNSPECIFIED PART
32	S310100	CLOSED FRACTURE SHAFT OF FEMUR
33	S310011	Thigh fracture NOS
34	S310012	Upper leg fracture NOS
35	S310100	Closed fracture shaft of femur
36	S310z00	Closed fracture of shaft or unspecified part, NOS
37	S311.00	OPEN FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART
38	S311000	OPEN FRACTURE OF FEMUR, UNSPECIFIED PART
39	S311100	OPEN FRACTURE SHAFT OF FEMUR
40	S311z00	OPEN FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART, NOS
41	S312.00	CLOSED FRACTURE DISTAL FEMUR
42	S312.11	CLOSED FRACTURE OF FEMUR, DISTAL END
43	S312000	CLOSED FRACTURE OF DISTAL FEMUR, UNSPECIFIED
44	S312100	Closed fracture of femoral condyle, unspecified
45	S312200	CLOSED FRACTURE OF FEMUR, LOWER EPIPHYSIS
46	S312300	CLOSED FRACTURE DISTAL FEMUR, SUPRACONDYLAR
47	S312400	CLOSED FRACTURE DISTAL FEMUR, MEDIAL CONDYLE
48	S312500	CLOSED FRACTURE DISTAL FEMUR, LATERAL CONDYLE
49	S312600	CLOSED FRACTURE DISTAL FEMUR, BICONDYLAR (T-Y FRACTURE)
50	S312x00	CLOSED FRACTURE DISTAL FEMUR, COMMINUTED/INTRA-ARTICULAR
51	S312z00	CLOSED FRACTURE OF DISTAL FEMUR NOT OTHERWISE SPECIFIED
52	S313.00	OPEN FRACTURE DISTAL FEMUR
53	S313.11	OPEN FRACTURE OF FEMUR, DISTAL END
54	S313000	OPEN FRACTURE DISTAL FEMUR, UNSPECIFIED
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S313100	OPEN FRACTURE OF FEMORAL CONDYLE, UNSPECIFIED
S313200	OPEN FRACTURE OF FEMUR, LOWER EPIPHYSIS
S313300	OPEN FRACTURE DISTAL FEMUR, SUPRACONDYLAR
S313400	OPEN FRACTURE DISTAL FEMUR, MEDIAL CONDYLE
S313500	OPEN FRACTURE DISTAL FEMUR, LATERAL CONDYLE
S313600	OPEN FRACTURE DISTAL FEMUR, BICONDYLAR (T-Y FRACTURE)
S313x00	OPEN FRACTURE DISTAL FEMUR, COMMINUTED/INTRA-ARTICULAR
S313z00	OPEN FRACTURE OF DISTAL FEMUR NOT OTHERWISE SPECIFIED
S314.00	FRACTURE OF SHAFT OF FEMUR
S315.00	FRACTURE OF LOWER END OF FEMUR
S31z.00	FRACTURE OF FEMUR, NOS
S3x2.00	MULTIPLE FRACTURES OF FEMUR
SC3D400	SEQUELAE OF FRACTURE OF FEMUR
Syu7200	[X]FRACTURES OF OTHER PARTS OF FEMUR

For Review Only

Table S2 online- List of benzodiazepines, DDD, and Half-life.

ATC code	Name	Defined Daily Dose DDD	Unit	Half-life*
N05B				
N05BA01	diazepam	10	mg	Long (>24)
N05BA02	chlordiazepoxide	30	mg	Long (>24)
N05BA03	medazepam	20	mg	Long (>24)
N05BA04	oxazepam	50	mg	Intermediate (8-24)
N05BA05	potassium clorazepate	20	mg	Long (>24)
N05BA06	lorazepam	2.5	mg	Intermediate (8-24)
N05BA07	adinazolam			Short (<8)
N05BA08	bromazepam	10	mg	Intermediate (8-24)
N05BA09	clobazam	20	mg	Intermediate (8-24)
N05BA10	ketazolam		mg	Intermediate (8-24)
N05BA11	prazepam	30	mg	Long (>24)
N05BA12	alprazolam	1	mg	Intermediate (8-24)
N05BA13	halazepam	0.1	g	Long (>24)
N05BA14	pinazepam		mg	Intermediate (8-24)
N05BA15	camazepam	30	mg	Intermediate (8-24)
N05BA16	nordazepam	15	mg	Long (24)
N05BA17	fludiazepam	0.75	mg	Long (>24)
N05BA19	etizolam		mg	Short (<8)
N05BA21	clotiazepam		mg	Short (<8)
N05CD				
N05CD01	flurazepam	30	mg	Long (>24)
N05CD02	nitrazepam	5	mg	Long(>24)
N05CD03	flunitrazepam	1	mg	Intermediate (8-24)
N05CD04	estazolam	3	mg	Intermediate (8-24)
N05CD05	triazolam	0.25	mg	Short(<8)
N05CD06	lormetazepam	1	mg	Intermediate(8-24)
N05CD07	temazepam	20	mg	Intermediate(8-24)
N05CD08	midazolam	15	mg	Short(<8)
N05CD09	brotizolam	0.25	mg	Short (<8)
N05CD10	quazepam	15	mg	Long(>24)
N05CD11	loprazolam	1	mg	Intermediate(8-24)
N05CF				
N05CF01	zopiclone*	7.5	mg	Short (<8)
N05CF02	zolpidem*	10	mg	Short (<8)
N05CF03	zaleplon	10	mg	Short (<8)
N05CM				
N05CM02	Clomethiazole	1.5	g	

\* **Half life** definitions: Short (<8); Intermediate (8-24), Long (>24)

Table S3 online – List of medication codes included as potential confounders

ATC code	
H02AB	Glucocorticoids
M05BA01	etidronic acid
M05BA02	clodronic acid
M05BA03	pamidronic acid
M05BA04	alendronic acid
M05BA05	tiludronic acid
M05BA06	ibandronic acid
G03XC01	raloxifene
H05AA	Parathyroid hormones and analogues
M05BX03	Strontium ranelate
A11CC04	calcitriol
A11CC05	colecalfiferol
	calcium+ colecalfiferol
A11CC06	calcifediol
H05BA	Calcitonin preparations
N06AA	Non-selective monoamine reuptake inhibitors
N06AB	Selective serotonin reuptake inhibitors
N05A	Antipsychotics
N05AA	Phenothiazine with aliphatic side-chain
N05AB	Phenothiazines with piperazine structure
N05AC	Phenothiazines with piperidine structure
N05AD	Butyrophenone derivatives
N05AE	Indole derivatives
N05AF	Thioxanthene derivative
N05AG	Diphenylbutylpiperidine derivatives
N05AH	Diazepines, oxazepines, thiazepines and oxepines
N05AL	Benzamides
N05AN	Lithium
N05AX	Other antipsychotics
N04	Anti-Parkinson drugs
N04A	Anticholinergic agents
N04AA	Tertiary amines
N04AB	Ethers chemically close to antihistamine
N04AC	Ethers of tropine or tropine derivatives
N04B	Dopaminergic agents
N04BA	Dopa and dopa derivatives
N04BB	Adamantane derivatives
N04BC	Dopamine agonists
N04BD	Monoamine oxidase B inhibitors
N04BX	Other dopaminergic agents
N03A	Antiepileptics
N03AA	Barbiturates and derivatives
N03AB	Hydantoin derivatives
N03AC	Oxazolidine derivatives
N03AD	Succinimide derivatives
N03AE	Benzodiazepine derivatives
N03AF	Carboxamide derivatives

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	N03AG	Fatty acid derivatives
	N03AX	Other antiepileptics
	R03BA	Glucocorticoids
	R03BA01	Beclometasone
	R03BA02	Budesonide
	R03BA03	Flunisolide
	R03BA04	Betamethasone
	R03BA05	Fluticasone
	R03BA06	Triamcinolone
	R03BA07	Mometasone
	R03BA08	Ciclesonide
	N05BB	Diphenylmethane derivatives (sedating)
	R03A	Adrenergics, inhalants
	R03AC	Selective beta-2-adrenoreceptor agonists
	R03AK	Adrenergics and other drugs for obstructive airway diseases
	R03C	Adrenergics for systemic use
	R03CC	Selective beta-2-adrenoreceptor agonists
	R03B	Other drugs for obstructive airway diseases, inhalants
	R03BB	Anticholinergics
	C01B	Antiarrhythmics, class I and III
	C01BA	Antiarrhythmics, class Ia
	C01BB	Antiarrhythmics, class Ib
	C01BC	Antiarrhythmics, class Ic
	C01BD	Antiarrhythmics, class III
	C09	Agents acting on the renin-angiotensin system
	C09A	ACE inhibitors, plain
	C09AA	ACE inhibitors, plain
	C09B	ACE inhibitors, combinations
	C09BA	ACE inhibitors and diuretics
	C09BB	ACE inhibitors and calcium channel blockers
	C09	Agents acting on the renin-angiotensin system
	C09C	Angiotensin II antagonists, plain
	C09CA	Angiotensin II antagonists, plain
	C09D	Angiotensin II antagonists, combinations
	C09DA	Angiotensin II antagonists and diuretics
	C09DB	Angiotensin II antagonists and calcium channel blockers
	C09DX	Angiotensin II antagonists, other combinations
	C07A	Beta blocking agents
	C07AA	Beta blocking agents, non-selective
	C07AB	Beta blocking agents, selective
	C07AG	Alpha and beta blocking agents
	C07B	Beta blocking agents and thiazides
	C07BA	Beta blocking agents, non-selective, and thiazides
	C07BB	Beta blocking agents, selective, and thiazides
	C07BG	Alpha and beta blocking agents and thiazides
	C07C	Beta blocking agents and other diuretics
	C07CA	Beta blocking agents, non-selective, and other diuretics
	C07CB	Beta blocking agents, selective, and other diuretics
	C07CG	Alpha and beta blocking agents and other diuretics
	C07D	Beta blocking agents, thiazides and other diuretics

C07DA	Beta blocking agents, non-selective, thiazides and other diuretics
C07DB	Beta blocking agents, selective, thiazides and other diuretics
C07F	Beta blocking agents and other antihypertensives
C07FA	Beta blocking agents, non-selective, and other antihypertensives
C07FB	Beta blocking agents, selective, and other antihypertensives
C08	Agents acting on the renin-angiotensin system
C08C	Selective calcium channel blockers with mainly vascular effects
C08CA	Dihydropyridine derivatives
C08CX	Other selective calcium channel blockers with mainly vascular effects
C08D	Selective calcium channel blockers with direct cardiac effects
C08DA	Phenylalkylamine derivatives
C08DB	Benzothiazepine derivatives
C08E	Non-selective calcium channel blockers
C08EA	Phenylalkylamine derivatives
C08EX	Other non-selective calcium channel blockers
C08G	Calcium channel blockers and diuretics
C08GA	Calcium channel blockers and diuretics
C02A	Antiadrenergic agents, centrally acting
C02AA	Rauwolfia alkaloids
C02AB	Methyldopa
C02AC	Imidazoline receptor agonists
C02C	Antiadrenergic agents, peripherally acting
C02CA	Alpha-adrenoreceptor antagonists
C02CC	Guanidine derivatives
C02D	Arteriolar smooth muscle, agents acting on
C02DA	Thiazide derivatives
C02DB	Hydrazinophthalazine derivatives
C02DC	Pyrimidine derivatives
C02DD	Nitroferricyanide derivatives
C02DG	Guanidine derivatives
C02K	Other non-selective calcium channel blockers
C02KA	Alkaloids, excluding rauwolfia
C02KB	Tyrosine hydroxylase inhibitors
C02KC	MAO inhibitors
C02KD	Serotonin antagonists
C02KX	Other antihypertensives
C02L	Calcium channel blockers and diuretics
C02LA	Rauwolfia alkaloids and diuretics in combination
C02LB	Methyldopa and diuretics in combination
C02LC	Imidazoline receptor agonists in combination with diuretics
C02LE	Alpha-adrenoreceptor antagonists and diuretics
C02LF	Guanidine derivatives and diuretics
C02LG	Hydrazinophthalazine derivatives and diuretics
C02LK	Alkaloids, excluding rauwolfia, in combination with diuretics
C02LL	MAO inhibitors and diuretics
C02LN	Serotonin antagonists and diuretics
C02LX	Other antihypertensives and diuretics
C03A	Low-ceiling diuretics, thiazides
C03AA	Thiazides, plain
C03AB	Thiazides and potassium in combination

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	C03AH	Thiazides, combinations with psycholeptics and/or analgesics
	C03AX	Thiazides, combinations with other drugs
	C03B	Low-ceiling diuretics, excluding thiazides
	C03BA	Sulfonamides, plain
	C03BB	Sulfonamides and potassium in combination
	C03BC	Mercurial diuretics
	C03BD	Xanthine derivatives
	C03BK	Sulfonamides, combinations with other drugs
	C03BX	Other low-ceiling diuretics
	C03C	High-ceiling diuretics
	C03CA	Sulfonamides, plain
	C03CB	Sulfonamides and potassium in combination
	C03CC	Aryloxyacetic acid derivatives
	C03CD	Pyrazolone derivatives
	C03CX	Other high-ceiling diuretics
	C03D	Potassium-sparing agents
	C03DA	Aldosterone antagonists
	C03DB	Other potassium-sparing agents
	C03E	Diuretics and potassium-sparing agents in combination
	C03EA	Low-ceiling diuretics and potassium-sparing agents
	C03EB	High-ceiling diuretics and potassium-sparing agents
	C03X	Other diuretics
	C03XA	Vasopressin antagonists
	G03C	Estrogens
	G03CA	Natural and semi synthetic estrogens, plain
	G03CX	Other estrogens
	G03D	Progestogens
	G03DA	Pregnen-(4) derivatives
	G03DC	Estren derivatives
	G03F	Progestogens and estrogens in combination
	G03FA	Progestogens and estrogens, fixed combinations
	G03FB	Progestogens and estrogens, sequential preparations
	H03A	Thyroid preparations
	H03AA	Thyroid hormones
	H03B	Antithyroid preparations
	H03BA	Thiouracils
	H03BB	Sulphur-containing imidazole derivatives
	H03BC	Perchlorates
	H03BX	Other antithyroid preparations
	M01CB03	Auranofin
	M01CB02	Sodium aurothiomalate
	M01CC01	Penicillamine
	P01BA01	Chloroquine
	P01BA02	Hydroxychloroquine sulphate
	L04AX01	Azathioprine
	L04AD01	Cyclosporine
	L04AA13	Leflunomide
	L01BA01/L01AX03	Methotrexate
	L04AA24	Abatacept
	L04AB04	Adalimumab



L04AC03	Anakinra
L04AB01	Etanercept
L04AB02	Infliximab
L01XC02	Rituximab
A07EC01	Sulfasalazine
A10BG	Thiazolidinediones
A10A	Insulins and analogues
A10AB	Insulins and analogues for injection, fast-acting
A10AC	Insulins and analogues for injection, intermediate-acting
A10AD	Insulins and analogues for injection, interm-acting combined with fast-acting
A10AE	Insulins and analogues for injection, long-acting
A10AF	Insulins and analogues for inhalation
A10B	Blood glucose lowering drugs, excluding insulins
A10BA	Biguanides
A10BB	Sulfonamides, urea derivatives
A10BC	Sulfonamides (heterocyclic)
A10BD	Combinations of oral blood glucose lowering drugs
A10BF	Alpha glucosidase inhibitors
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10BX	Other blood glucose lowering drugs, excluding insulins
A10X	Other drugs used in diabetes
A10XA	Aldose reductase inhibitors
A03F	Propulsives
A03FA	Propulsives
A03FA01	Metoclopramide
B01AA	Vit K antagonist
B01AB	Heparin group
N02A	Opioids
N02AA	Natural opium alkaloids
N02AB	Phenylpiperidine derivatives
N02AC	Diphenylpropylamine derivatives
N02AD	Benzomorphan derivatives
N02AE	Oripavine derivatives
N02AF	Morphinan derivatives
N02AG	Opioids in combination with antispasmodics
N02AX	Other opioids
M01AA	Butylpyrazolidines
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other antiinflammatory and antirheumatic agents, non-steroids
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin



C10AA07	rosuvastatin
C10AA08	pitavastatin
A02BC01	omeprazole
A02BC02	pantoprazole
A02BC03	lansoprazole
A02BC04	rabeprazole
A02BC05	esomeprazole
L02BG	Enzyme inhibitors
L02BG01	aminoglutethimide
L02BG02	formestane
L02BG03	anastrozole
L02BG04	letrozole
L02BG05	vorozole
L02BG06	exemestane

For Review Only

Table S4 online- Co-morbidity and co-medication at case and control moments in BIFAP and CPRD. Case-crossover study

	BIFAP				CPRD			
	Cases date N=5,412		Crude OR	95% CI	Cases date N=12,853		Crude OR	95% CI
	n	%			n	%		
<b>Co-morbidities (anytime before case moment)</b>								
Previous fractures ((including hip/femur and any other)	1010	18.66	NA	NA	2149	16.72	NA	NA
Rheumatoid arthritis (not including osteoporosis)	80	1.48	NA	NA	239	1.86	NA	NA
Osteoporosis	844	15.59	NA	NA	1101	8.57	NA	NA
Paget's disease	24	0.44	NA	NA	34	0.26	NA	NA
Anaemia	879	16.24	NA	NA	1058	8.23	NA	NA
Epilepsy/Seizures	94	1.74	NA	NA	301	2.34	NA	NA
Syncope	665	12.29	NA	NA	530	4.12	NA	NA
Ischaemic heart disease	661	12.21	NA	NA	1142	8.89	NA	NA
Cerebrovascular disease	617	11.40	NA	NA	1072	8.34	NA	NA
Malignant neoplasms	731	13.51	NA	NA	1369	10.65	NA	NA
Inflammatory bowel disease	30	0.55	NA	NA	106	0.82	NA	NA
Obstructive airway disease	423	7.82	NA	NA	921	7.17	NA	NA
Liver disease	136	2.51	NA	NA	156	1.21	NA	NA
Chronic renal failure	254	4.69	NA	NA	131	1.02	NA	NA
Mental disorders (without depression)	139	2.57	NA	NA	334	2.6	NA	NA
Dementia and/or Alzheimers	566	10.46	NA	NA	895	6.96	NA	NA

Co-medication	BIFAP						CPRD					
	N	%	N	%	Crude OR	95% CI	N	%	N	%	Crude OR	95% CI
	Cases date N=5,412		∑controls* (date1-4) N=20,029		Crude OR	95% CI	Cases date N=12,853		∑control* (date1-4) N=48,382		Crude OR	95% CI
Glucocorticoids >3months	97	1.79	304	1.52	1.72	1.17-2.54	173	1.35	564	1.17	173	1.35
Glucocorticoids (inhaled)	113	2.09	467	2.33	0.67	0,46-0,96	293	2.28	1220	2.52	293	2.28
Bisphosphonate use	304	5.62	1092	5.45	1.26	0,97-1,65	459	3.57	1430	2.96	459	3.57
Raloxifene	22	0.41	81	0.40	1.11	0,41-3,01	10	0.08	37	0.08	10	0.08
Strontium danelate	11	0.20	56	0.28	0.48	0,15-1,49	20	0.16	46	0.10	20	0.16
Parathyroid hormone	9	0.17	16	0.08	14.24	1,65-122,94	0	0.00	0	0.00	0	0.00
Calcium & Vitamin D	451	8.33	1638	8.18	1.12	0,93-1,34	765	5.95	2301	4.76	765	5.95
Calcitonin	54	1.00	172	0.86	1.39	0,89-2,16	2	0.02	8	0.02	2	0.02
Antidepressants	1332	24.61	4511	22.52	1.72	1,49-1,98	1580	12.29	5318	10.99	1580	12.29
Antipsychotics/lithium	481	8.89	1511	7.54	1.54	1,30-1,83	901	7.01	2924	6.04	901	7.01
Anti-Parkinsons drugs	262	4.84	911	4.55	1.97	1,28-3,02	268	2.09	930	1.92	268	2.09
Anticonvulsants	463	8.56	1562	7.80	1.52	1,23-1,88	474	3.69	1584	3.27	474	3.69
Bronchodilators	526	9.72	1915	9.56	1.11	0,92-1,34	782	6.08	2972	6.14	782	6.08
Antihypertensives	2615	40.00	8203	40.96	0.95	0,84-1,09	2334	18.16	9055	18.72	2334	18.16
Diuretics	1385	25.59	5110	25.51	1.11	0,97-1,27	1990	15.48	7573	15.65	1990	15.48
Anti-arrhythmics	131	2.42	421	2.10	1.90	1,17-3,09	146	1.14	533	1.10	146	1.14

<b>Sedating antihistamines</b>	67	1.24	229	1.14	1.22	0,84-1,78	33	0.26	108	0.22	33	0.26
<b>Estrogen-containing hormone replacement therapy (HRT)</b>	10	0.18	36	0.18	1.16	0,38-3,50	75	0.58	318	0.66	75	0.58
<b>Thyroid hormones</b>	205	3.79	726	3.62	1.53	1,03-2,26	597	4.64	2229	4.61	597	4.64
<b>Antithyroid drugs</b>	23	0.42	86	0.43	1.07	0,44-2,62	20	0.16	61	0.13	20	0.16
<b>Disease-modifying anti-rheumatic drugs (DMARDs)</b>	42	0.78	177	0.88	0.80	0,42-1,50	107	0.83	406	0.84	107	0.83
<b>Thiazolidinediones</b>	22	0.41	73	0.36	2.02	0,76-5,38	37	0.29	137	0.28	37	0.29
<b>Other antidiabetics</b>	718	13.27	2842	14.19	0.68	0,54-0,85	423	3.29	1587	3.28	423	3.29
<b>Antiemetic (Metoclopramide)</b>	83	1.53	260	1.30	1.24	0,93-1,64	117	0.91	364	0.75	117	0.91
<b>Anticoagulants</b>	509	9.41	1574	7.86	1.96	1,62-2,37	309	2.40	1168	2.41	309	2.40
<b>Morphine/opiates</b>	613	11.33	1860	9.29	1.88	1,61-2,20	1373	10.68	4424	9.14	1373	10.68
<b>=&gt;2 prescriptions for a non-steroidal anti-inflammatory drug (NSAID)</b>	514	9.50	2079	10.38	0.85	0,74-0,98	440	3.42	1634	3.38	440	3.42
<b>Statins</b>	680	12.56	2675	13.36	0.87	0,70-1,06	1199	9.33	4548	9.40	1199	9.33
<b>Proton pump inhibitors</b>	2015	37.23	6920	34.55	1.56	1,40-1,74	1681	13.08	5863	12.12	1681	13.08
<b>Aromatase inhibitors</b>	34	0.63	141	0.70	0.77	0,35-1,69	64	0.50	223	0.46	64	0.50

\*Sum of controls columns report number of control moments exposed to each co-morbidity.

NA: Non-applied due to the matching by patient.