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

Journal:	*Pharmacoepidemiology and Drug Safety*
Manuscript ID:	PDS-14-0399.R2
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	27-May-2015
Complete List of Authors:	Requena, Gema; University of Alcala, Pharmacology, Biomedical Sciences Logie, John; GlaxoSmithKline, Worldwide Epidemiology Martin, Elisa; Spanish Agency of Medicines and Medical Devices, BIFAP Research Unit Boudiaf, Nada; GlaxoSmithKline, Worldwide Epidemiology González González3, Rocío; Spanish Agency of Medicines and Medical Devices, BIFAP Research Unit Huerta, Consuelo; Spanish Agency of Medicines and Medical Devices, BIFAP Research Unit Alvarez, Arturo; Spanish Agency of Medicines and Medical Devices, BIFAP Research Unit Webb, David; GlaxoSmithKline, Worldwide Epidemiology Bate, Andrew; Pfizer, Epidemiology García Rodríguez, Luis; CEIFE, Centro Español de Investigación Farmacoepidemiológica Reynolds, Robert; Pfizer, Epidemiology Schlienger, Raymond; Novartis Pharma, AG Gardarsdottir, Helga; Utrecht University, Pharmacoepidemiology & Clinical Pharmacology de Groot, Mark; Utrecht University, Pharmacoepidemiology & Clinical Pharmacology Klungel, Olaf; Utrecht University, Pharmacoepidemiology & Clinical Pharmacology de Abajo, Fancisco; University of Alcalá, Department of Biomedical Sciences; University Hospital Principe de Asturias, Clinical Pharmacology Unit Douglas, Ian; LSHTM, Epidemiology
Keywords:	Case crossover, Self-controlled case series, benzodiazepines, hip fractures, electronic healthcare records database
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, 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.

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

Running head: A comparison across case-only designs and databases.

Authors: *G Requena*[*1], *J Logie*[*2], *E Martín*[3], *N Boudiaf*[2], *R González-González*[3], *C Huerta*[3], *A Alvarez*[3], *D Webb*[2], *A Bate*[4], *LA Garcia-Rodríguez*[5], *R Reynolds* [6], *R Schlienger*[7], *H Gardarsdottir*[8], *M de Groot*[8], *OH Klungel* [8] , *F de Abajo*[1,9] *and I J Douglas*[10].

***Authors contributed equally**

Affiliation:

1. Pharmacology Unit, Department of Biomedical Sciences, School of Medicine, University of Alcalá, Madrid , Spain
2. Worldwide Epidemiology, GlaxoSmithKline Research and Development, Stockley Park West, Uxbridge, Middlesex, UK
3. BIFAP Research Unit, Spanish Agency of Medicines and Medical Devices, Madrid, Spain
4. Epidemiology, Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, UK
5. Spanish Center for Pharmacoepidemiological Research (CEIFE), Madrid, Spain
6. Epidemiology, Pfizer Research & Development, New York, USA
7. Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland
8. Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands
9. Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain
10. London School of Hygiene and Tropical Medicine (LSHTM), London, UK

Author for correspondence:

Gema Requena
Facultad de Medicina y Ciencias de la Salud
Universidad de Alcalá
Ctra. Madrid-Barcelona, km 33.2
28871 Alcalá de Henares
Madrid, Spain
Email address: requenagema@gmail.com

Key words: Case crossover (CXO); Self-controlled case series (SCCS); Benzodiazepines; hip fractures; electronic healthcare records databases (DBs).

Key points: 1- Case-only designs may offer better control for time invariant confounding factors than traditional designs and may be a useful choice when intrinsic factors may represent relevant confounding.

2- Care is needed to ensure the underlying assumptions of these designs are met and to interpret the results obtained as they may not always generalise to patients receiving continuous treatment with the medication being assessed.

3- In the SCCS design, it is important to explore the potential event-exposure dependence as even temporary effects can have a large impact on results.

4- This research has shown that performing multi-site studies, using a common protocol provides useful comparisons across countries and across designs.

Specific author contribution:

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

Financial support:

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

Potential competing interests:

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

JL, DW and NB are employees and stockholders of GlaxoSmithKline.

RS is a Novartis employee and owns Novartis shares.

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

IJD consults for and holds stock in GSK, and consults for Gilead.

Acknowledgements:

The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency. The paper is on behalf of WP2 (members can be found at introduction of the special issue).

The authors would like to thank the excellent collaboration of physicians in the participating countries, whose contribution in recording their professional practice with high quality standards makes possible the availability of DBs used in this research.

Word Count main text: 3,334

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

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 [1]. 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 [2].

The case crossover (CXO) method was developed by Maclure (1991), to investigate the risk of transient and immediate acute events [3]. 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[4]. Hence, the intermittency of drug use and the length of the exposure time window may have an impact on the estimates obtained [2]. 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 [5].

The self-controlled case series (SCCS) method was developed by Farrington (1995) to study the association between vaccination and adverse events [6]. 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 [7].

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

methodology. As a case study we used the well-established association[8,9] of benzodiazepines and related drugs (BZD) with hip/femur fractures (HFF). BZD are often used intermittently and with these case-only designs some confounding such as frailty could be addressed.

The present research was undertaken within the frame of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT) project (http://www.imi-protect.eu/).

PATIENTS AND METHODS

The study was performed in two primary care DBs: The UK Clinical Practice Research Datalink (CPRD GOLD) [10], and "Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria" (BIFAP) from Spain. These DBs have been described in detail elsewhere [11]. The protocol was registered in The European Network of Centres for Pharmacoepidemiolgy and Pharmacovigilance, ENCePP [12]. A blinding procedure was maintained until results were made available to the coordinating centre at Utrecht University, the Netherlands.

Study population

The study period was considered from the 1st January 2001 until 31st December 2009. All data were used when the practices were considered "Up to (research) Standard" (a marker of data quality). Patients who had at least one year of registration with the general practitioner (GP), were ≥18 years old, and were 12 months free of HFF were included in the study population. All patients were required to have a recorded diagnosis of HFF during the study period, i.e. they were all "cases". For the SCCS, patients were required to have 6 months free of BZD prescriptions before entering the study to restrict the population to new users. This criterion was not applied for the CXO to ensure all case or control moments had the opportunity to be exposed to BZD. Patients could enter at any time they fulfilled the criteria above. The start date was the date patients met the cited criteria.

Case definition

HFF was searched in the BIFAP database using the International Classification of

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

Exposure definition

BZD was the exposure of interest, comprising all those classified as anxiolytics, hypnotics and related drugs in the Anatomical Therapeutic Chemical (ATC) classification[15]. (Supplementary Table S2 online). Related drugs (Z-drugs and clomethiazole) were included in this research because their therapeutic actions are similar to benzodiazepines[16].

Duration of each prescription was estimated based on the prescribed amount and daily dose. The expected duration of use was calculated following the methods of Gardarsdottir et al[17]. When a gap of more than 30 days occurred between the theoretical end date of a prescription and the date of the subsequent prescription, exposure was considered to be discontinuous, and a new treatment episode was considered.

The person-time of each patient was divided according to their exposure into periods of current, recent, past and non-use. Thus, current use was the period from the start of a BZD prescription until 30 days after the estimated end date of the supply; recent use was the period up to 60 days after current use; past use was the period after recent use until the patient became exposed again or the end of follow-up; non-use was the period between the start date and the first BZD prescription within the study period. Combined non-use and past use was considered the reference category or baseline (Figure 1). For the SCCS, current use was further divided into five risk time windows: 1-30, 31-60, 61-182, 183-365 and >365 days. BZD are thought to increase the risk of fractures during

the early stages of treatment[18,19] and this was taken into account when defining exposure time windows.

For the CXO, each case serves as its own control, and up to four control moments were defined at 91, 182, 273 and 365 days prior to the HFF (case moment). This method assumes that the baseline risk for an exposure is constant, and this assumption was tested using up to four control periods per case, improving the precision of the effect size, and the efficiency by using the whole year prior to the event[20].

For each patient, exposure at the case moment was compared to exposure at control moments. In addition for this design, the current use period was further categorized as single use of anxiolytics, single use of hypnotics, and use of both.

Potential confounders

These studies are part of a common protocol where four analytical study designs were performed to investigate the same study question (http://www.encepp.eu/encepp/viewResource.htm?id=6179).

In the CXO, all medications mentioned in the protocol (See Table S3 online) were considered as potential confounders. Indicator terms for medication use were added to the model denoting the absence or presence of prescriptions of each separate type of medication listed in Table S3, within the 91 days prior to the case or control moments.

In the SCCS, age was considered as the most important potential confounder, given its strong association with fracture risk[21] and given that many relevant unmeasured factors are likely to be age-related (e.g. frailty or increase in severity of underlying diseases) as well as related to BZD pattern of use.

Analysis

Analyses in BIFAP were performed using Stata®-11, in CPRD analyses were performed using SAS v9.2 for the CXO and Stata®-10 for the SCCS.

In the CXO, conditional logistic regression was used to estimate the relative risk in terms of ORs with corresponding 95% confidence intervals (CI).

In the SCCS, conditional Poisson regression was used to estimate the relative risk in terms of incidence rate ratios (IRRs) with corresponding 95% CI[22].

To examine potential event-exposure dependence, a pre-exposure time risk window was created in the SCCS with a length of 30 days, allowing us to examine whether an incident HFF has a short term impact on the likelihood of being prescribed a BZD. IRR were estimated excluding this pre-exposure time of 30 days from the reference category in a sensitivity analysis.

RESULTS

Case Crossover

Characteristics of study populations (BIFAP and CPRD)

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

Effect of BZD (BIFAP and CPRD)

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

Effect of BZD treatment duration in CPRD

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 model accounting for duration class did not provide a significantly better fit to the data than one considering presence/absence of BZD exposure alone (chi-square for comparison of –2log L scores = 6.82, DF = 4, p = 0.15) (Figure 3).

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[13].

CXO study

Crude and AORs were similar between databases. Other CXO studies showed similar associations. Neutel et al [23], for example, found a crude OR = 1.7, 95%CI: 1.0-2.9, for exposure to BZD and Berry et al [24] 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 [13]. As falls and fractures are dose-related adverse effects [25], 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[13].

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 [22] 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 [14] 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'[26], 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[27,28], 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

BZD (e.g. confounding by contraindication). This confounding would lead to an underestimate of the relative risk of HFF associated with BZD use. In case-only designs, time invariant confounding factors are implicitly controlled for by design, although a confounding by transient changes in other factors cannot be excluded.

The fact that the cohort/NCC analyses were restricted to BZD users with a reference category of past-use, and therefore, all patients were exposed at least once to the drug of interest, made the comparison between cohort members more similar than if an external cohort of non-users had been used. In contrast, a reference category of non-use was appropriate for the case-only analyses, as differences between persons are removed by design.

Results obtained with both case-only designs were similar, although the precision of the estimates was higher in the SCCS than in the CXO which may be consider as potential advantage of the former.

The experience of comparing different designs using the same source population is limited. The study of Madigan et al[29], part of the Observational Medical Outcomes Partnership (OMOP) project, studied this drug-event pair employing a SCCS and a cohort design within the same data source, and compared the results across ten DBs. Seven out of ten DBs found no increased risk of HFF associated with BZD use, when a SCCS was employed. However, this study was not specific to BZD-HFF, and explored 53 drug-event pairs under a surveillance perspective rather than specifically addressing this pair in a formal hypothesis testing study with a pair specific protocol.

There are some publications comparing designs yielding different results, although studying different associations[30,31]. In most articles, relative risk estimates with case only designs were lower than those obtained with cohort or NCC designs, with authors generally concluding that the higher estimates obtained using these designs may be due to between-person confounding.

Strengths and limitations

We only had access to prescribing data, rather than the precise dates on which medication was actually taken. It is therefore possible that exposure periods are misclassified to some extent, with both exposed and unexposed periods affected to some

degree. The effect of this would tend to bias results towards the null, and so it is possible that we have underestimated any real effect of treatment with BZD.A major strength of this research is the use of a common protocol allowing the use of harmonized methods and definitions across DBs, aiding the direct comparison of results.

In general, case-only designs are limited by their underlying assumptions. In this study, the assumption of independence between event and exposure in the SCCS design was not met but was subsequently corrected for by the use of a pre-exposure risk period[22].

In our case only two DBs have been employed with just one drug-event association, so results might not be extrapolated to other settings and certainly not be generalised to other drug-event pairs.

CONCLUSIONS

CXO designs yielded consistent results across DBs. Once we accounted for the event-exposure dependence, estimates derived from SCCS were also consistent across DBs and across designs. Case-only designs may offer better control for time invariant confounding factors than traditional designs and are a useful choice when intrinsic factors may represent relevant confounding, and when the effects of transient exposures are to be measured. Care is needed to ensure the underlying assumptions of these designs are met and to interpret the results obtained as they may not always generalise to patients receiving continuous treatment with the medication being assessed.

These studies together with the cohort and case control analyses have shown that performing multi-site studies using a common protocol provides useful comparisons across countries and across designs, contributing to a better understanding of potential differences between pharmacoepidemiological studies used to assess drug safety.

REFERENCES

1. Smeeth L, Donnan PT, Cook DG. The use of primary care databases: case-control and case-only designs. *Fam Pract.* Oct 2006;23(5):597-604.
2. Delaney JA, Suissa S. The case-crossover study design in pharmacoepidemiology. *Stat Methods Med Res.* Feb 2009;18(1):53-65.
3. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol.* Jan 15 1991;133(2):144-153.
4. Hebert C, Delaney JA, Hemmelgarn B, Levesque LE, Suissa S. Benzodiazepines and elderly drivers: a comparison of pharmacoepidemiological study designs. *Pharmacoepidemiol Drug Saf.* Aug 2007;16(8):845-849.
5. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. *Vaccine.* May 7 2004;22(15-16):2064-2070.
6. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Statistics in medicine.* May 30 2006;25(10):1768-1797.
7. Farrington CPaW, H. J. Semiparametric analysis of case series data. *Journal of the Royal Statistical Society.* Nov 2006 2006;55(5):553-594.
8. Ray WA, Griffin MR, Downey W. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA.* Dec 15 1989;262(23):3303-3307.
9. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS Drugs.* 2003;17(11):825-837.
10. Williams T vsT, Puri S, et al. . Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource *Therapeutic Advances in Drug Safety.* 2012;3 (2):89-99
11. Abbing-Karahagopian V, Kurz X, de Vries F, et al. Bridging Differences in Outcomes of Pharmacoepidemiological Studies: Design and First Results of the Protect Project. *Curr Clin Pharmacol.* Nov 11 2013.
12. ENCePP ENoCfPaP. ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance). http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed Oct 2012.
13. Requena G, Huerta C, Gardarsdottir H, et al. Hip/femur fractures associated with the use of BZDs (benzodiazepines anxiolytics, hypnotics and related drugs): A methodological approach to assess consistencies across databases. *Pharmacoepidemiol Drug Safety.* 2015(Supplement).
14. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res.* Jun 2000;15(6):993-1000.
15. WHO CCfDSM. Anatomical Therapeutic Chemical (ATC) Classification system. 2013; http://www.whocc.no/atc_ddd_index/. Accessed September, 2014.
16. Terzano MG, Rossi M, Palomba V, Smerieri A, Parrino L. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Saf.* 2003;26(4):261-282.
17. Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. *J Clin Epidemiol.* Apr 2010;63(4):422-427.
18. Zint K, Haefeli WE, Glynn RJ, Mogun H, Avorn J, Sturmer T. Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture

associated with benzodiazepine use in older adults. *Pharmacoepidemiol Drug Saf.* Dec 2010;19(12):1248-1255.
19. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. *Am J Psychiatry.* Jun 2001;158(6):892-898.
20. Mittleman MA, Maclure M, Robins JM. Control sampling strategies for case-crossover studies: an assessment of relative efficiency. *Am J Epidemiol.* Jul 1 1995;142(1):91-98.
21. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone.* Dec 2001;29(6):517-522.
22. Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol.* Mar 15 2009;169(6):761-768.
23. Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. *Pharmacoepidemiol Drug Saf.* Mar 2002;11(2):97-104.
24. Berry SD, Lee Y, Cai S, Dore DD. Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents. *JAMA internal medicine.* May 13 2013;173(9):754-761.
25. File SE. Behavioural pharmacology of benzodiazepines. *Prog Neuropsychopharmacol Biol Psychiatry.* 1984;8(1):19-31.
26. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *Journal of general internal medicine.* May 2011;26(5):546-550.
27. Maclure M, Fireman B, Nelson JC, et al. When should case-only designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf.* Jan 2012;21 Suppl 1:50-61.
28. Maclure M. 'Why me?' versus 'why now?'--differences between operational hypotheses in case-control versus case-crossover studies. *Pharmacoepidemiol Drug Saf.* Aug 2007;16(8):850-853.
29. Madigan D, Ryan PB, Schuemie M, et al. Evaluating the impact of database heterogeneity on observational study results. *Am J Epidemiol.* Aug 15 2013;178(4):645-651.
30. Douglas IJ, Evans SJ, Hingorani AD, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ.* 2012;345:e4388.
31. Ravera S, van Rein N, de Gier JJ, de Jong-van den Berg LT. A comparison of pharmacoepidemiological study designs in medication use and traffic safety research. *Eur J Epidemiol.* Jun 2012;27(6):473-481.

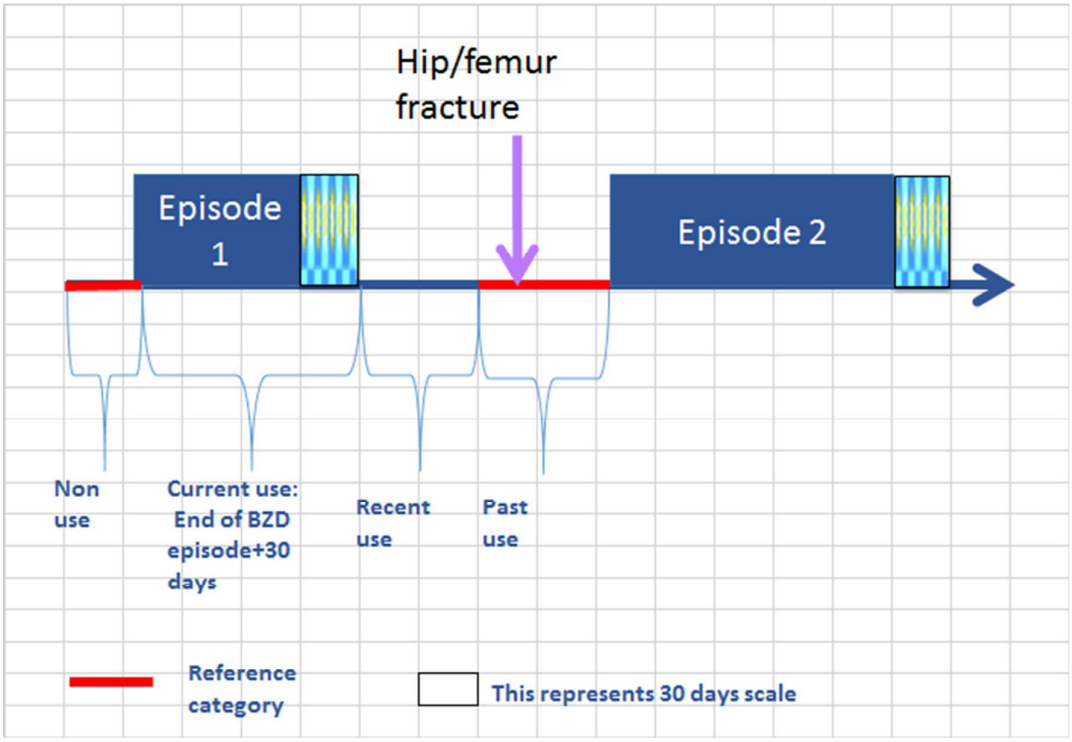
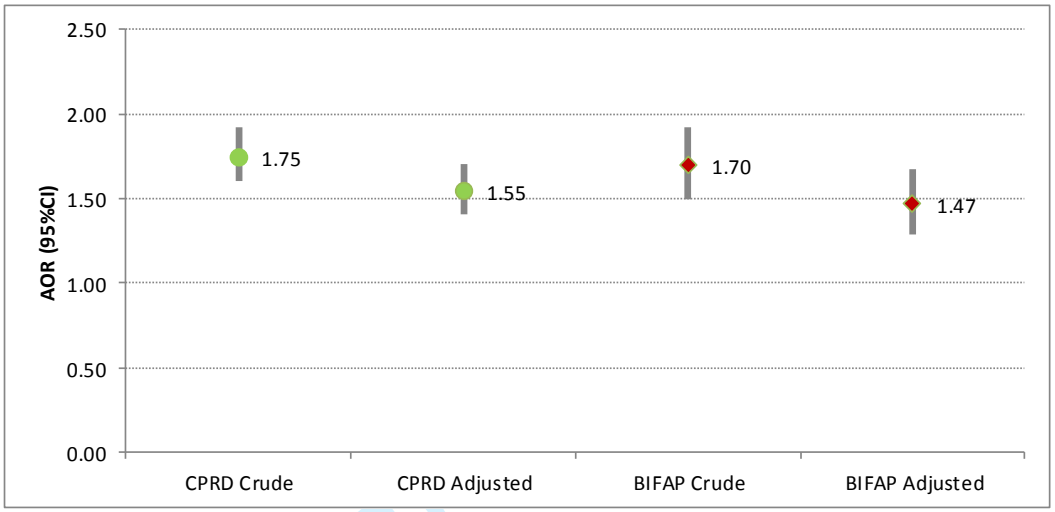


Figure 1. Structure of exposure definition. The follow-up continued beyond the date of hip/femur fracture only for the SCCS.

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

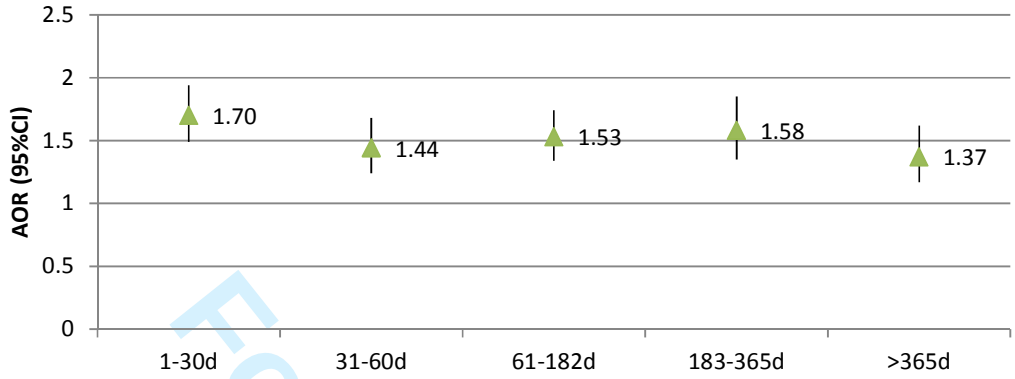
	Number of cases with M controls (N%)		Number of cases with at least M controls (N%)	
Control Moments(M)	**CPRD**	**BIFAP**	**CPRD**	**BIFAP**
1	530 (4.1)	267 (4.7)	12,853 (100)	5,412 (100)
2	474 (3.7)	272 (4.8)	12,323 (95.9)	5,145 (95.1)
3	492 (3.8)	274 (4.8)	11,849 (92.2)	4,873 (90.0)
4	11,357 (88.4)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

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)
∑controls, 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%)	
Past/Non-use	2,615	5,169,915	1.00	-	-	1.00	-	-	6,060	15,769,427	1.00	-	-	1.00	-	-
Recent use	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
Current use	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
1-30 days	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
31-60 days	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
61-182 days	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
183-365 days	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
>365 days	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

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)							
			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%)	
Past/Non-use	1,898	4,941,912	1.00	-	-	1.00	-	-	5,549	15,344,912	1	-	-	1	-	-
Recent use	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
Current use	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
1-30 days	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
31-60 days	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
61-182 days	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
183-365 days	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
>365 days	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
Pre-exposure period	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

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology ISPE

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. *Please delete as necessary* Yes ~~NO~~ N/A

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

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. Yes ~~NO~~ ~~N/A~~

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~~

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

---

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.

Andrew Bate is an employee and shareholder of Pfizer

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)

Andrew Bate

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

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

ARTURO ALVAREZ GUTIERREZ

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):
POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:
POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

Consuelo Huerta

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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

---

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.

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) project has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Association) companies' in-kind contribution. As a special form of the IMI JU grant, Utrecht University and University of Alcalá received a direct financial contribution from Pfizer and Astra-Zeneca, respectively. JL, DW, NB, RS, AB and RR belong to EFPIA member companies in the IMI JU and costs related to their part in the research were carried by the respective company as in-kind contribution under the IMI JU scheme. The views expressed are those of the authors only and not of their respective institution or company.

---

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)

Dave Webb

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

October 2011

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

Elisa Martín

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

FRANCISCO J. DE ABAJO

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. No

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

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. No

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) project has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Association) companies' in-kind contribution. As a special form of the IMI JU grant, Utrecht University and University of Alcalá received a direct financial contribution from Pfizer and Astra-Zeneca, respectively. JL, DW, NB, RS, AB and RR belong to EFPIA member companies in the IMI JU and costs related to their part in the research were carried by the respective company as in-kind contribution under the IMI JU scheme. The views expressed are those of the authors only and not of their respective institution or company.

---

8. Manuscript title (first six words are sufficient)

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)

Gema Requena

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

October 2011

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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

---

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.

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) project has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Association) companies' in-kind contribution.

---

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)

Helga Gardarsdottir

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

Ian Douglas

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. No

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

3. The sponsor of this project had the right of final editing and/or approval of the manuscript submitted. No

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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

---

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.

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) project has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Association) companies' in-kind contribution. As a special form of the IMI JU grant, Utrecht University and University of Alcalá received a direct financial contribution from Pfizer and Astra-Zeneca, respectively. JL, DW, NB, RS, AB and RR belong to EFPIA member companies in the IMI JU and costs related to their part in the research were carried by the respective company as in-kind contribution under the IMI JU scheme. The views expressed are those of the authors only and not of their respective institution or company.

---

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)

John Logie

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

October 2011

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

luis alberto garcia rodriguez

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

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

---

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)

Mark de Groot

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

Nada Boudiaf

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) project has received support from the Innovative Medicines Initiative Joint Undertaking (IMI JU) (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Association) companies' in-kind contribution. As a special form of the IMI JU grant, Utrecht University and University of Alcalá received a direct financial contribution from Pfizer and Astra-Zeneca, respectively.

The division of Pharmacoepidemiology & Clinical Pharmacology employing O.H. Klungel received Top Institute Pharma Grant T6.101 Mondriaan unrestricted grant for pharmacoepidemiological research.

---

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)

Olaf Klungel

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

October 2011

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. Yes

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

October 2011

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

---

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.

RR is an employee and shareholder of Pfizer, Inc. The views expressed herein are those of the authors and not necessarily those of Pfizer, Inc.

---

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)

Robert F. Reynolds

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

This form is available online by clicking here

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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. No

---

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.

---

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)

Rocío González González

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

This form is available online by clicking here

October 2011

PDS Pharmacoepidemiology & Drug Safety
Official Journal of the International Society for Pharmacoepidemiology

CONFLICT OF INTEREST DISCLOSURE

The Editors of *Pharmacoepidemiology and Drug Safety* recognize that most studies in pharmacoepidemiology cost money and thus pose a potential conflict of interest. As a conflict of interest may affect the assessment or judgment of an author, we ask that **all** authors (not just the Corresponding Author) complete the following form.

For Co-authors: Please complete questions 4-10. Completed forms should be saved, and emailed as an attachment to the Corresponding Author.

For Corresponding Authors: Please complete all questions. It is the responsibility of the Corresponding Author to submit completed forms on behalf of all co-authors via Manuscript Central at the point of manuscript submission.

Corresponding author only (Co-authors go to Question 4):

POTENTIAL STUDY INTERPRETATION CONFLICTS

1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a

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

---

Corresponding author and Co-authors:

POTENTIAL FINANCIAL CONFLICTS

4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No

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

October 2011

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

---

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. ☒

This form is available online by clicking here

October 2011

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

CODES	HIP/FEMUR FRACTURES
ICPC-2	
L75	Fracture: femur
READ	**HIP FRACTURES**
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

S302z00	Cls # of proximal femur, pertrochanteric section, NOS
S303.00	OPEN FRACTURE OF PROXIMAL FEMUR, PERTROCHANTERIC
S303011	OPEN FRACTURE OF FEMUR, GREATER TROCHANTER
S303012	OPEN FRACTURE OF FEMUR, LESSER TROCHANTER
S303100	OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, TWO PART
S303200	OPEN FRACTURE PROXIMAL FEMUR, SUBTROCHANTERIC
S303300	OPEN FRACTURE PROXIMAL FEMUR, INTERTROCHANTERIC, COMMINUTED
S303400	OPEN FRACTURE OF FEMUR, INTERTROCHANTERIC
S303z00	OPEN FRACTURE OF PROXIMAL FEMUR, PERTROCHANTERIC, NOS
S304.00	PERTROCHANTERIC FRACTURE
S305.00	SUBTROCHANTERIC FRACTURE
S30w.00	CLOSED FRACTURE OF UNSPECIFIED PROXIMAL FEMUR
S30x.00	OPEN FRACTURE OF UNSPECIFIED PROXIMAL FEMUR
S30y.00	CLOSED FRACTURE OF NECK OF FEMUR NOS
S30y.11	HIP FRACTURE NOS
S30z.00	OPEN FRACTURE OF NECK OF FEMUR NOS
S4E..00	FRACTURE-DISLOCATION OR SUBLUXATION HIP
S4E0.00	CLOSED FRACTURE-DISLOCATION, HIP JOINT
S4E1.00	OPEN FRACTURE-DISLOCATION, HIP JOINT
S4E2.00	CLOSED FRACTURE-SUBLUXATION, HIP JOINT
S4E3.00	OPEN FRACTURE-SUBLUXATION, HIP JOINT
READ	**FEMUR FRACTURES**
7K1G200	Primary open reduction+external fixation of femoral fracture
7K1L500	CLOSED REDUCTION OF FRACTURE OF FEMUR
K7805F	REDUCTION CLOSED FRACTURE FEMUR
K7815F	REDUCTION OPEN FRACTURE FEMUR
S31..00	OTHER FRACTURE OF FEMUR
S310.00	CLOSED FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART
S310000	CLOSED FRACTURE OF FEMUR, UNSPECIFIED PART
S310100	CLOSED FRACTURE SHAFT OF FEMUR
S310011	Thigh fracture NOS
S310012	Upper leg fracture NOS
S310100	Closed fracture shaft of femur
S310z00	Closed fracture of shaft or unspecified part, NOS
S311.00	OPEN FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART
S311000	OPEN FRACTURE OF FEMUR, UNSPECIFIED PART
S311100	OPEN FRACTURE SHAFT OF FEMUR
S311z00	OPEN FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART, NOS
S312.00	CLOSED FRACTURE DISTAL FEMUR
S312.11	CLOSED FRACTURE OF FEMUR, DISTAL END
S312000	CLOSED FRACTURE OF DISTAL FEMUR, UNSPECIFIED
S312100	Closed fracture of femoral condyle, unspecified
S312200	CLOSED FRACTURE OF FEMUR, LOWER EPIPHYSIS
S312300	CLOSED FRACTURE DISTAL FEMUR, SUPRACONDYLAR
S312400	CLOSED FRACTURE DISTAL FEMUR, MEDIAL CONDYLE
S312500	CLOSED FRACTURE DISTAL FEMUR, LATERAL CONDYLE
S312600	CLOSED FRACTURE DISTAL FEMUR, BICONDYLAR (T-Y FRACTURE)
S312x00	CLOSED FRACTURE DISTAL FEMUR, COMMINUTED/INTRA-ARTICULAR
S312z00	CLOSED FRACTURE OF DISTAL FEMUR NOT OTHERWISE SPECIFIED
S313.00	OPEN FRACTURE DISTAL FEMUR
S313.11	OPEN FRACTURE OF FEMUR, DISTAL END
S313000	OPEN FRACTURE DISTAL FEMUR, UNSPECIFIED

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

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	colecalciferol
	calcium+ colecalciferol
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

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

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

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	%		
Co-morbidities (anytime before case moment)								
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

	BIFAP						CPRD					
Co-medication	**N**	**%**	**N**	**%**			**N**	**%**	**N**	**%**		
	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

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