Signal detection for recently approved products: Adapting and Evaluating Self-Controlled Case Series Method using a US Claims and UK EMR Database

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Short Title

Self-Controlled Case Series Method for signal detection in healthcare databases
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Abstract

Background: The Self-Controlled Case Series (SCCS) method has been widely used for hypothesis testing, but there is limited evidence of its performance for safety signal detection.

Objective: To evaluate SCCS for signal detection on recently approved products.

Methods: A retrospective study covered the period after 3 recently marketed drugs were launched through Dec 31st, 2010 using The Health Improvement Network (THIN), a UK primary care database, and Optum, a US claim database. SCCS method was applied to examine 5 heterogenous outcomes with desvenlafaxine and escitalopram and 6 outcomes with adalimumab for Signals of Disproportional Recording (SDRs) - lower 95% bound of incidence rate ratio (IRR) estimate greater than 1. Multiple design choices were tested and the trend in IRR estimates over calendar time for one drug event pair was examined.

Results: All 6 outcomes with adalimumab, 3 of 5 outcomes with desvenlafaxine, and 4 of 5 outcomes with escitalopram had SDRs. SCCS highlighted all acute events in the primary analysis but was less successful with slower onset outcomes. Performance varied by risk period definition. Changes in IRR estimates over quarterly intervals for adalimumab showed an SDR within 9 months of drug launch.

Conclusion: SCCS shows promise for signal detection: It may highlight known associations for recent marketed products and with potential for early signal identification. SCCS performance varied by design choice and nature of both exposure and event pair. Future work is needed to determine how effective the approach is in prospective testing and determining performance characteristics of the approach.

Key points

- SCCS is a promising approach for signal detection in real world data, highlighting known associations for products with limited time of market penetration.
- SCCS may offer potential for early signal identification of drug safety.
- SCCS provides most promising performance with the design choices of “new case” as case definition and “Exposure duration” approach for defining risk period, as well as the applications for acute events.
1. Introduction

Secondary use of electronic healthcare records (EHR) including electronic medical records (EMRs) and insurance claims data for hypothesis testing studies has been done for many decades [1–4]. Signal detection activities to identify potential drug safety issues has historically focused primarily on spontaneous reports[5], but more recently EHRs have also been investigated for their utility [6–10].

The Self-Controlled Case Series (SCCS) method, proposed by Farrington (1995) [11], is widely used for assessing vaccine and drug safety for formal hypothesis testing studies [12–16] and there is growing interest in its potential application with EHR data for signal detection [7, 10, 17–22]. A central challenge in signal detection method development is testing performance[5]. Much of the testing of SCCS has been against reference sets developed by Observational Medical Outcome Partnership (OMOP) [7, 10, 18–22]. OMOP testing showed promising characteristics of the SCCS method, with performance assessed as similar, or better, than other methods [19, 22]. One similarity across all reference sets is their overwhelming focus on established medicinal products. It is not clear that findings on established products generalize to newer molecular entities. For a newly marketed medicine, its product uptake, the changes in the patient characteristics and drug utilization pattern over time will be different from mature products [19], thus, it is necessary to explore how the performance of SCCS is applied to a newer medical product.

In this study, we implemented SCCS in a signal screening framework for three relatively new drugs to the market: Humira (Adalimumab, AbbVie Inc., Chicago, US; FDA approval in Dec 2002 and EMA approval in September 2003), Pristiq (desvenlafaxine, Pfizer Inc., New York, US; FDA approval in Feb 2008), and Lexapro (Escitalopram oxalate, Forest Laboratories, Inc., St. Louis, US; FDA approval in Aug 2002 and EMA approval in June 2002).

2. Method

2.1 Study design

This study is a retrospective active surveillance database study. The study covers the period after each study drug was launched through Dec 31st, 2010. We chose to study drugs that have been marketed for several years as this means they have a well-established safety profile. However, we would also be able to assess the performance of safety surveillance during the period of early marketing. Specifically, the study period is 1/1/2002- 12/31/2010 for Adalimumab; 2/1/2007 -12/31/2010 for desvenlafaxine; 8/1/2001-12/31/2010 for escitalopram in OPTUM; and 6/1/2001 -12/31/2010 for escitalopram in THIN to allow 12 month enrolment for those patients entered in the database right after the drug approval date.
All patients having valid data in the databases during the study period were eligible for inclusion.

2.2 Data sources

This study used The Health Improvement Network (THIN), a UK EMR database, and Optum, a US claim database.

THIN data contains de-identified primary care EMR data provided by IMS Health [23]. THIN data covers ~6% of the population in the UK and is broadly representative. It holds comprehensive demographic, clinical and prescribing data. The September 2011 version of THIN data was used for this analysis, which covers ~9 million unique patients.

Optum is a longitudinal US claims database from United Healthcare (UHC) insurance plans that represents approximately 3–4% of the geographically diversified population in US [24]. The database contains longitudinal de-identified patient data that include registration, pharmacy claims, medical claims, inpatient and outpatient services utilization, and procedures, and lab results. The 2010 Q4 version was used for the analysis which covers ~44 million unique patients.

2.3 Exposure

Much signal detection testing has focused on screening relatively large numbers of drug-outcome pairs and looked at quantitative performance of characteristics compared to external reference sets rather than extensive evaluation of the pairs [10, 18-19, 21-22]. We therefore decided to look in depth at a small number of drug-outcome pairs with a focus on an area of relatively recent therapeutic innovation. To help with generalizability, we initially selected two medications in two different therapeutic areas: desvenlafaxine, an antidepressant drug, and adalimumab, a rheumatoid arthritis (RA) drug with a focus on RA indication. At planning stage we anticipated both drugs would be well captured in both Optum and THIN databases. When we initiated the study we discovered that the coverage was limited to the US Claims for desvenlafaxine. Upon further analysis it became clear that no bDMARDs were well captured in THIN so we elected to not conduct a THIN SCCS analysis on adalimumab. For transparency we elected to continue to study these two drugs using Optum database but to also include some similar drugs that were captured in both databases. Thus, escitalopram was added to the study using both THIN database and Optum database.

National Drug Code (NDC), a US drug coding system, was used for defining the exposures in Optum data and BNF codes/ Mulitlex codes, a UK drug coding system, were used for defining the exposures in THIN data.

2.4 Outcome
Five outcomes were selected for studying the association with desvenlafaxine and escitalopram: Hypertension, Orthostatic hypotension, Proteinuria, Hyperlipidemia, and Fractures (All types). Six outcomes were selected for studying the association with adalimumab: Acute Myocardial Infarction (AMI), GI Perforation, Herpes Zoster, Interstitial Lung Disease, Lymphoma, and Pneumonia. The rationale of selecting the outcomes includes general importance to drug safety, inclusion of the outcomes in the product label, literature of safety concerns in the same drug class (antidepressants - fracture), and feasibility for studying the outcomes using Optum or THIN data. Specifically, we first selected the events of interests for desvenlafaxine and adalimumab, two drugs initially planned to be studied. All events for these two drugs were labelled except for fracture with desvenlafaxine which was discussed in the literature as a safety concern in the same drug class [25-28]. As escitalopram, an antidepressant, was added later to allow the use of both databases, we have kept the same events of interest for this drug same as for desvenlafaxine. The outcomes were defined using ICD-9 codes in Optum data (Table 1, Electronic Supplementary Material (ESM) #1 and READ codes in THIN data (Table 2, ESM #1).

2.5 Analysis Methods

The SCCS model assuming events arise from a non-homogeneous Poisson process includes individuals who have had both the exposure and outcome of interest regardless of the timing and order of exposure and outcome [10, 15, 18-19, 22, 29]. SCCS method does not require a reference exposure group, as each patient is both exposed and unexposed and acts as their own reference for comparison, which implicitly controls for time-fixed covariates. Incidence rate ratios (IRR) are calculated by comparing the rate of events in a given post-exposure period (risk period) to the rate of events in unexposed periods absent of the exposure (all other observed time) [15-16]. In a signal screening framework, statistical uncertainty is examined based on the 95% confidence interval of the IRR estimates. Specifically, when the lower 95% bound of IRR estimate is greater than 1 (i.e. $\text{IRR}_{0.025} > 1$) this is considered a positive finding and is a Signal Of Disproportional Recording (SDR) analogous to SDRs in spontaneous reporting which are findings of potential interest that have not undergone clinical review to be considered signals of suspected causality [30-31]. Key assumptions for SCCS method include conditionally independent events and events conditionally independent of exposure. Accurate dating of outcomes is also important, and we acknowledge some of the outcomes included here are difficult to date e.g. lymphoma and hyperlipidemia. Nonetheless, they are included to test the resilience of the method to this assumption, as there is a lack of evidence about the impact of violating SCCS assumptions. The details of SCCS method has been described extensively elsewhere [15, 18-19]. We
implemented SCCS (Figure 1.) using OMOP standard SAS programming procedures as developed by the researchers of Columbia University and published on OMOP’s website for this study [32]. The code was further modified as needed for all analyses conducted here, including the ‘Exposure Duration’ approach using SAS 9.2 version.

2.6 Design Choices

The selection of analytic design choices would impact the implementation of the SCCS method testing [19, 33]. For this study, the design choices selected for the primary and secondary analyses are summarized in Table 1.

We only looked at the 1st occurrence of each outcome of interest to capture incident event in this study. We then focused on the events with the requirement of a 12 month event free enrolment period (defined as “New” cases) in the primary analysis. In a secondary analysis, we also investigated the events without the requirement of a 12 month event free enrolment period (defined as “All cases”), recognizing that this selection means we may sometimes include events that are not incident [34]. The “All Case” definition was included in the OMOP SCCS package.

In a drug safety signal detection framework, appropriate risk period selection may differ from a formal hypothesis-testing study in epidemiology. There is limited literature on the impact of such selection on method performance for signal detection, although OMOP conducted some initial evaluation. Two approaches to risk period selection are compared. 1). “OMOP” approach (Figure 2.1 – 2.5): risk period is defined as exposure start plus 30 days (fixed period), and exposure duration plus a variable subsequent period (0, 30, 60 or 90 days) thus, 5 risk periods are selected and all other time is considered baseline (varied by risk period). The risk period “exposure duration plus 30 days within the end of exposure” was selected in the primary analysis, allowing the risk of an outcome to be elevated at any time during exposure as well as the 30 day initial surveillance window. 2) A modified approach - “Exposure Duration” approach (Figure 3): risk period is exposure duration. Three 30 day washout periods (1-30, 31-60, 61-90 days) after estimated end of exposure are analyzed separately as potential exposure windows where the drug effects may still exist. Risk and washout periods are each compared with the same baseline to obtain incidence rate ratio (IRR) estimates. Initiation of a new medication tends to occur on the day a patient visits their doctor. Patients will often notify their doctor of recent medical events at the same visit, and therefore events recorded on the date a new medication is started will often predate the start of treatment. Thus, the first day of treatment is not included in risk time, to minimize misclassification errors.
As another secondary analysis, we also examined the change in IRR estimates over calendar
time from SCCS model using the parameters in the primary analysis through a single drug
event pair highlighted with a high IRR during the first phase of analyses to better understand
if observational data might be used for earlier signal identification.

3. Results

An overview of the demographic characteristics of the patients included in the analysis per
drug-outcome pair is presented in Table 2. Total number of patients per drug-outcome varied
by nature of the outcome (i.e. rare or common), database, and length of drug on the market.
The most common outcomes in this analysis are hyperlipidemia and hypertension while the
least common outcomes are AMI and lymphoma. Overall, females had higher proportion of
the conditions than males except for AMI, and average age at 1st drug exposure is similar to
the average age at 1st condition.

3.1 Primary Analysis

Figure 4 shows results for all exposures and outcomes using the primary approach. All 6
outcomes of interest (i.e. AMI, GI perforation, Herpes zoster, interstitial lung disease,
lymphoma, and pneumonia) associated with adalimumab were highlighted as potential safety
concerns with IRR$>1$ or SDR. Three of the 5 outcomes of interest (i.e. Fractures,
orthostatic hypotension, and proteinuria) were found to have SDRs associated with
desvenlafaxine (i.e. IRR$>1$). Two pairs without SDRs were: Hypertension and
hyperlipidemia. For Escitalopram, except for hypertension, 4 outcomes (i.e. fractures,
hyperlipidemia, orthostatic hypotension, and proteinuria) had SDR on both THIN and Optum
data. Hypertension had no SDR in neither THIN nor Optum. The IRR and 95% CI for each
of these drug-outcome pairs are listed in Table 3.

3.2 Secondary Analysis

Choice of Case Inclusion Criteria

Figure 5 shows the comparison of the results of “All Cases” and “New Cases”. When using
criteria of “All Cases”, the SCCS method not only produced consistent lower estimates
across all drug-outcome pairs and databases, but also fewer SDRs. For “all cases”, SCCS
highlighted 50% of outcomes of interest (3 pairs) associated with adalimumab on Optum
data, none of outcomes of interest associated with desvenlafaxine on Optum data, and 40% of
outcomes of interest (2 pairs) associated with escitalopram on both THIN and Optum data.
Choice of Risk Periods

Figure 6 indicates that SCCS method performance varied by the choice of risk periods when using the OMOP approach. In general, a major difference was seen when defining the exposed period as the first 30 days of drug exposure (i.e. fixed period) only: 60% or more estimates on adalimumab, desvenlafaxine, and escitalopram in Optum data, and 40% of estimates on escitalopram in THIN data were smaller than seen in the primary analysis. Increasing the number of days included in the risk period post-treatment led to an increase in IRR estimates of the majority of pairs in Optum data.

As shown in Figure 7 “Exposure Duration” approach generated often higher estimates of the IRR in the 1st or 2nd washout period compared with those when risk period was the estimated duration of treatment alone. For example, consistently higher estimates of the IRR during the “first washout period” than risk period as well as other wash out periods were observed across 6 adalimumab- outcome pairs. However, the estimate of the IRR was generally lower in the final washout period (days 61-90) than during exposure. Wider 95% CI of the estimates in the 3 washout periods were observed due to fewer events counted as incident cases.

Comparing the IRR estimates between the OMOP and Exposure Duration approaches (across figures 6 and 7 respectively) where the risk period were both set as exposure duration only, the Exposure Duration approach generated consistently higher estimates for all 6 adalimumab - outcome pairs and highlighted one more SDR (i.e. lymphoma); the estimates for the Exposure Duration approach were either similar to or slightly higher than those obtained with the OMOP approach for the desvenlafaxine and escitalopram – outcome pairs. Neither method identified escitalopram and hypertension (THIN or Optum); nor desvenlafaxine and hypertension or desvenlafaxine and hyperlipidemia (Optum).

We observed that the Exposure Duration approach highlighted 5 pairs (i.e. Herpes Zoster, Lymphoma, and Pneumonia with adalimumab; Orthostatic Hypotension with desvenlafaxine; and Orthostatic Hypotension with escitalopram in Optum ) with IRR≥2 while no pair with IRR≥2 was found using “OMOP” approach regardless the selection of the OMOP risk periods. While direction of IRR was similar, in general, across the two approaches, some discordance from these two approaches was observed. For example the Exposure Duration approach identified a SDR (i.e. IRR>1) of hypertension with escitalopram in Optum during the 1st and 2nd washout period while no SDR was seen with the OMOP approach.

Risk over time
Figure 8 shows results of IRR of herpes zoster in patients using adalimumab since drug launch to end of 2010. This example allows us to see the changes of IRR over time for this drug-outcome pair and understand if observational data may be used for earlier signal identification. Overall, IRR were all greater than 1 over time. There were no cases reported in the 1st quarter of the 1st year after the drug approval date. However, the IRR estimates in the following three quarters since the drug launch were substantially higher though the event numbers were low (IRR=6.15 in 2003 Q2 and IRR=4.40 in 2003 Q4). The estimates continued the decline over next two years from IRR=3.35 in 2004 Q1 to IRR=2.01 in 2006 Q2 before they were stabilized during the period from 2006 Q2 to 2010 Q4 with an IRR of approximate 2.0 for all estimates.

4. Discussion

Our findings suggest that SCCS may be useful for safety signal detection in EHRs; most known adverse drug reactions associated with desvenlafaxine and escitalopram for depression and adalimumab for RA were correctly identified in the framework we implemented using both THIN and Optum data. It also appears that early identification of previously unknown safety signals may be possible shortly after a new product is launched. The IRR estimates were partly dependent on design choices with respect to defining the “at risk” period.

The self-controlled case series can be implemented in many different ways in terms of time at risk, control time and wash out periods (i.e. neither control nor exposed time) and as it is also volatile to time varying confounding and other factors these design choices were anticipated to affect signal detection capability greatly.

This study builds on previous work by OMOP by assessing drugs near their time of launch, and by focussing on a few specific drug-event pairs, some of which we anticipated SCCS should perform well on, and some not, we have been able to uncover more insights into the applicability of the SCCS and its implementation for signal detection.

The vast majority of pairs were highlighted in the primary analysis. In particular, SCCS was able to highlight all acute events in the primary analysis. We would not normally expect to use SCCS to study chronic condition with uncertain onset date. However, our highlighting of adalimumab- lymphoma, an event in the black box warnings for adalimumab, supports a position that the method may sometimes be robust when the signal is very strong even though some assumptions are violated [35-36]. Future work needs to determine how effective the approach is for highlighting the previously unaccepted drug event pairs and determining performance characteristics of the approach including the robustness in handling
the chronic diseases for which the assumptions for the SCCS method might be violated. Hypertension and hyperlipidemia for desvenlafaxine were consistently not highlighted. Both are outcomes with slow onset that can only be identified through testing, requiring a visit to the general practitioner (GP) to have taken place. Escitalopram shares the same pattern for hypertension and the SDR of hyperlipidemia-Escitalopram was weak. We observed similar patterns for Escitalopram in both THIN and Optum: both of which are outcomes we anticipated SCCS would not be suitable for.

We selected labelled outcomes for the RA drug adalimumab and antidepressant desvenlafaxine, as well as fracture for desvenlafaxine, an outcome widely associated with antidepressants and widely studied in secondary databases studies [25-28]. We selected the same outcomes for escitalopram as for desvenlafaxine for comparability. Outcomes were selected to have varying properties (acute vs. chronic etc) and with varying evidential support for capability of accurate capture in Claims and EMRs. We note that five pairs (Herpes Zoster, Lymphoma, and Pneumonia with Adalimumab; Orthostatic Hypotension with desvenlafaxine; and Orthostatic Hypotension with escitalopram in Optum) were all highlighted by the “Exposure Duration” approach with an IRR≥2. Some argue that observational studies are more reliable when estimates greater than 2 are achieved [37-39], and in signal detection ranking based on SDR is often used to prioritise of pairs for further consideration [5].

In spontaneous reporting quantitative analysis it is well established that highlighted pairs require clinical review to be considered signals of suspected causality [5]. Outputs from quantitative signal detection in longitudinal observational databases similarly require further investigation to be considered signals as the coarse design choices required for implementation in a signal detection framework mean that many of the biases prevalent in observational data will not have been adequately controlled for.

In testing case inclusion criteria we found that solely including new cases in the case definition gave higher IRR estimates than including ‘all cases’. This is not surprising as cases close to registration are not always incident, but reflect recording of previous events or prevalent conditions [34]. While it is accepted that studying new cases rather than ‘all cases’ is appropriate in pharmacoepidemiological studies, we considered it worth investigating in a signal detection context because the dilution effect of including prevalent events might have been outweighed by the extra power of including more cases. The results however support the idea that the flawed “all case” design leads to lower estimates due to the inclusion of events recorded around the time of patient registration. As these events tend more often to occur during baseline periods of observation time, they will lead to an overestimate of the baseline event rate and hence would bias estimates of relative effects in a way that would make exposed time appear less harmful or even beneficial. Therefore we recommend for signal detection that ‘new cases’ should be used for SCCS signal detection.
In terms of risk period selection our results support a position that there is no uniformly appropriate exposure time and baseline time in a signal detection framework [33]. Overall, our results suggest that taking an “Exposure Duration” approach to defining the risk period and separate consideration of wash out periods performs well. However the finding that elevated IRR estimates representing SDRs were found during the wash out periods including sometimes 60-90 days, suggests that wash out period inclusion is of importance. SCCS studies have used wash out periods of, for example, 75 or 91 days [28,40] to include this apparent post-treatment period which can include some ongoing exposure. Our results suggest that the “Exposure Duration” risk period selection offers good potential for signal detection as it optimizes the distinction between exposed (high risk) time and baseline time. This would explain the larger effect estimates seen with the Exposure Duration approach compared with the OMOP approach as it is less likely that a risk period will erroneously include unexposed time, or the baseline includes time with persisting drug effect.

When examining the change in IRR estimate over quarterly intervals across the study period for adalimumab with herpes zoster we see that the estimate is immediately positive, albeit with wide confidence intervals, and then settles to a lower but still positive estimate. The significantly higher IRR in the first couple years since launch might indicate volatility of estimates newly after approval or a bias towards more recording of clinical events in people taking newly licensed treatments. In the package insert created in September 26 2003, other infrequent serious adverse events occurring at an incidence of less than 5% in patients treated with adalimumab in clinical trial included herpes zoster [41]. However, the frequency of the event in placebo group was not reported or compared and it could be interpreted that the causal nature of the event was uncertain at this stage. The finding that all drugs in this class are associated with an increased risk of herpes zoster was published until 2009 [42]. This suggests the potential of the SCCS method for early signal detection and the potential value in monitoring drug safety sequentially in longitudinal observational databases. Tracking the date when specific adverse reactions are added in the label would be helpful to evaluate the usefulness of SCCS for prospective, early signal detection.

A limitation of the study was that we focused our analysis on a more extensive analysis of a small number of drug event pairs for only a handful of drugs, which limits generalizability. We didn’t look at any negative control outcomes, so we can’t comment on specificity – further work will need to assess the number of false positive findings from the approach. While SCCS method implicitly controls time invariant variables, we did not adjust age or other time varying covariates in the model. From a signal detection perspective, inclusion of fewer covariates is often reasonable or preferred [43] as confounders and effect modifiers are unknown and can be better treated in post-hoc analyses. For relatively long observation periods, could easily be added to the model. Key assumptions for the SCCS method include conditionally independent events and events conditionally independent of exposure. While
selecting first incident event in the analysis helps satisfy the assumption of “conditionally independent events”, the assumption of “events conditionally independent of exposure” is likely violated (at least for some of pairs) as it is difficult to expect any event of interest does not have an impact on the future exposure of interest in the study. Nonetheless, if the effect on subsequent exposure is short lived the impact on effect estimates may not be great. Our results support a perspective that different approaches are needed when considering different outcomes and potentially which methods should be used to best detect emerging signals.

Much in the same way research suggests that some outcomes are more suited to detection in spontaneous reports and others in longitudinal observational databases [8]; similarly outcomes could be stratified into groups with similar properties (acute vs. chronic, transient vs. persistent, etc.), and signal detection approaches targeted at the specific groups individually, using a similar approach to epidemiological design proposed by mini- Sentinel [44]. In order to conduct method testing and better understand the capabilities of SCCS for signal detection, we have focused on a detailed analysis of labelled effects. In practice as hypothesis free signal detection for unexpected effects is increasingly conducted some further triage to focus most efforts on discovering outcomes often anticipated to have most public health importance and be reliably - or more effectively - detected in longitudinal observational databases may be warranted (e.g. those with biological plausibility, common ADRs, outcomes listed in risk management plans as potential safety concerns etc.). One example is using the SNIP criteria proposed for filtering spontaneous reports [45], focusing on WHO Critical terms [46] or those proposed as of particular value to screen for in previous longitudinal observation data research initiatives [9].

5. **Conclusion**

Our work shows that Self Controlled Case Series is a promising approach for signal detection, highlighting known associations for products with limited time for market penetration. We have shown which design choices look most promising and reaffirmed that performance of the Self Controlled Case series varies by the nature of both exposure and event pair and their anticipated association; this impact being important to consider in signal detection where there is necessarily less scope for tailored analyses. Future work needs to determine how effective the approach is for highlighting the previously unaccepted drug event pairs and determining performance characteristics of the approach.
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Compliance with Ethical Standards

This study was funded by Pfizer Inc. Xiaofeng Zhou, Rongjun Shen and Andrew Bate are full time employees of Pfizer Inc and hold stock and stock options. Pfizer manufactures one of the drugs studied herein: desvenlafaxine, as well as other products used to treat primary indications of the other two drugs analyzed herein, namely depression and rheumatoid arthritis. Ian Douglas is a full time employee of London School of Hygiene and Tropical Medicine and received no funding from Pfizer for his contribution to this study and manuscript. He is funded by an unrestricted grant from, holds stock in, and has consulted for, GlaxoSmithKline
References


34. Lewis J, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database – Pharmacoepidemiology and drug safety 2005; 14: 443–451
37. Ryan P, Highlights from the Observational Medical Outcomes Partnership’s (OMOP) Annual Symposium, Brookings Roundtable on Active Medical Product Surveillance, August 8, 2012; http://omop.org
44. Gagne JJ, Nelson JC, Fireman B. Taxonomy for monitoring methods within a medical product safety surveillance system: year two report of the Mini-Sentinel Taxonomy Project Workgroup
46. Lindquist M, Edwards IR, Bate A, Fucik H, Nunes AM, Ståhl M. From association to alert—a revised approach to international signal analysis. Pharmacoepidemiology and drug safety 1999 Apr 1;8(S1)