# MINI-SENTINEL METHODS DEVELOPMENT

# CASE-BASED METHODS WORKGROUP REPORT

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

**ABBREVIATIONS:**

| | |
|---|---|
| AE | Adverse Event |
| BLR | Bayesian Logistic Regression |
| CCAE | MarketScan® Commercial Claims And Encounters database |
| CCO | Case-Crossover |
| CI | Cholinesterase Inhibitors |
| CMLE | Conditional Maximum Likelihood Estimate |
| CTC | Case-Time-Control |
| CVT | Cardiovascular Thrombotic |
| DTP | Diphtheria-Tetanus-Pertussis Vaccine |
| DTaP | Diphtheria-Tetanus-acelluar Pertussis Vaccine |
| HDPS | High-Dimensional Propensity Score |
| HOI | Health Outcome of Interest |
| ICTPD | Information Component Temporal Pattern Discovery |
| LOD | Longitudinal Observational Database |
| MDCD | MarketScan® Medicaid Multi-State Database |
| MDCR | MarketScan® Medicare Supplemental Database |
| MMR | Measles-Mumps-Rubella Vaccine |
| MI | Myocardial Infarction |
| MSCCS | Multivariate Self-Controlled Case Series |
| MSLR | MarketScan® Lab Database |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OMOP | Observational Medical Outcomes Partnership |
| OR | Odds Ratio; Exposure Odds Ratio |
| PD-SCCS | Positive Dependence Self-Controlled Case Series |
| PDS | Pharmacoepidemiology and Drug Safety |
| RR | Relative Risk |
| SAS | Statistical Analysis System |
| SCCS | Self-Controlled Case Series |
| SRS | Spontaneous Reporting Systems |
| SSA | Sequence Symmetry Analysis |
| SSRI | Selective Serotonin Re-uptake Inhibitors |
| USCCS | Univariate Self-Controlled Case Series |

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# I. INTRODUCTION

The Mini-Sentinel Case-based Methods Workgroup met throughout 2010 and engaged in several projects. The first addressed the following question: When should a distributed system for active medical product surveillance use case-based designs for safety monitoring? Section II(A) presents our findings.

Another project focused specifically on self-controlled case series (SCCS) methods. Our SCCS work considered a multivariate extension of the SCCS approach; this work was done in collaboration with the Observational Medical Outcomes Partnership (OMOP). A complete SAS module for multivariate SCCS is now available on the OMOP website. Section II(B) of this report describes the method and some of our results.

Section II(C) presents our recommendations for Mini-Sentinel.

We also surveyed the recent SCCS literature. Section III presents the findings of our literature review.

The Appendix presents visualizations developed by Malcolm Maclure that are designed to provide insights into different forms of cases-based methods and the application of these methods. While the Workgroup had little time to discuss the pictures in sufficient depth to reach consensus on their utility, they were found to be interesting enough to include as suggestions in our report. The related comments are also suggestions rather than Workgroup conclusions.

# II. THE SELF-CONTROLLED CASE SERIES

## A. WHEN SHOULD A DISTRIBUTED SYSTEM FOR ACTIVE MEDICAL PRODUCT SURVEILLANCE USE CASE-BASED DESIGNS FOR SAFETY MONITORING?

To address this question, our workgroup a) defined case-based designs in relation to each other; b) examined their main strength: self-controlled comparisons; c) described the major difference among the designs: directionality; and d) discussed the range of medical products studied with these designs in relation to their susceptibility to exposure misclassification.

### 1. Definitions and Illustrations

The defining feature of *case-based* designs is that the *study base* is restricted to cases. Also in these designs, each subject serves as his or her own self-matched control, hence the term '*self-controlled*' [1-3]. The term '*crossover*' arises when the study base is restricted to subjects who supply both exposed and unexposed person-time and thus 'cross over' between two or more exposure levels [4, 5].

*Figure 1* shows the relationship between the self-controlled case series (SCCS) and case-crossover (CCO) designs, using data from *Table 2* in "Tutorial in Biostatistics: The self-controlled case series method" by Whitaker et al. [2] The figure shows the times when 10 children i) received Measles-Mumps-Rubella vaccinations, ii) passed through a hypothesized 14-day *induction period* after the vaccination, iii) then through a hypothesized 21-day *effect period* (respectively called the 'pre-risk period' and the 'risk period' by Whitaker et al., terms that are potentially ambiguous when discussing non-zero risks in the

'pre-risk' and 'post-risk' periods), and iv) the day they were diagnosed with meningitis. In the top half, the times are expressed in terms of the child's age in days, and the data are viewed, as in a SCCS, like a cohort of 10 children followed through their second year after birth. In the bottom half, the times are relative to the day of meningitis diagnosis, and the data are viewed retrospectively from the standpoint of the diagnosticians, as in a CCO analysis.

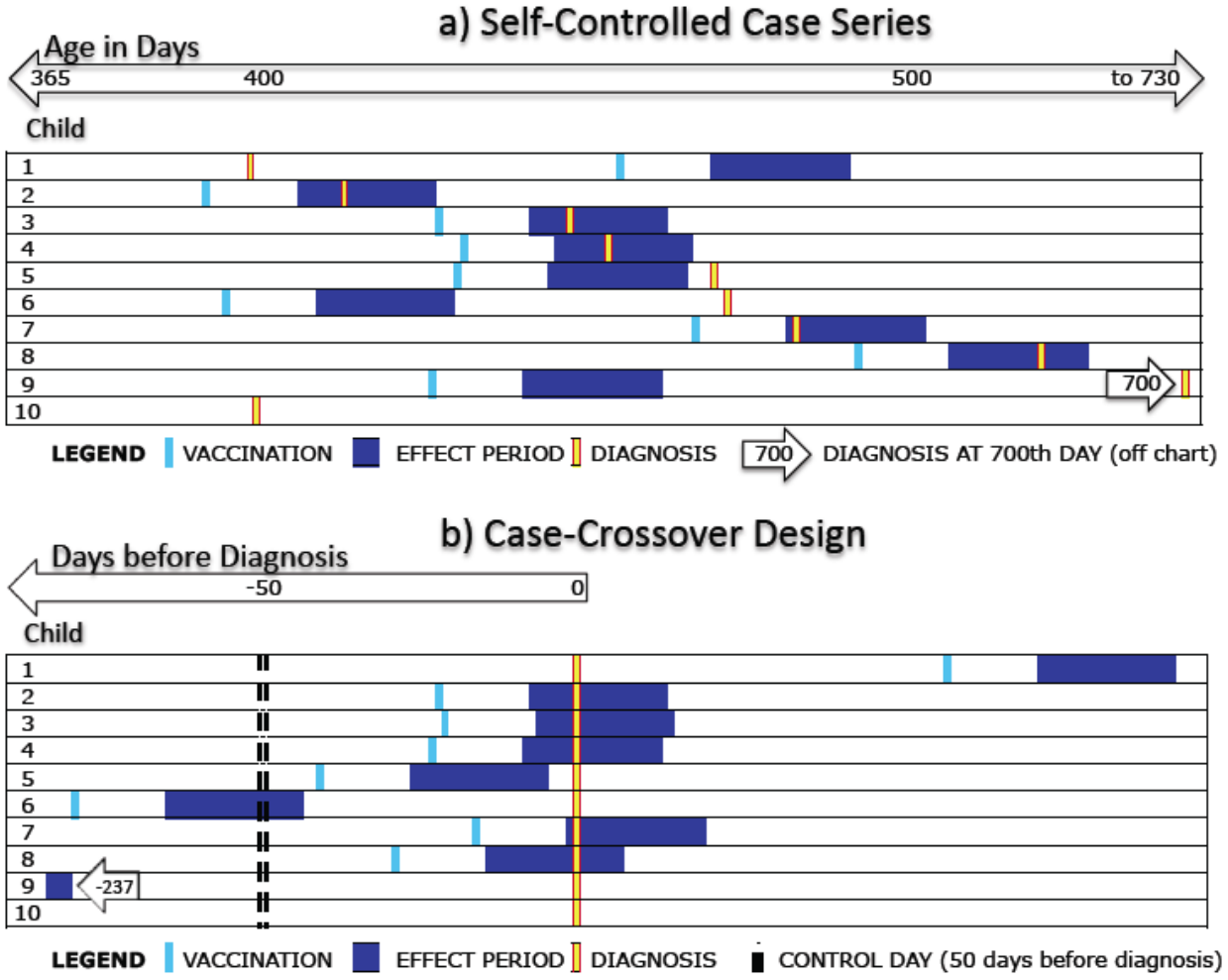


**Figure 1.** Comparison of time scales of a) self-controlled case series and b) case-crossover designs, using data on measles-mumps-rubella vaccination and viral meningitis from Whitaker HJ et al. Tutorial in biostatistics: the self-controlled case series method. *Statistics in Medicine* 2006;25:1768-97.

*Figure 2* shows the same data re-aligned so vaccination date is time zero. A small epidemic of meningitis is visible in the After period that is very unlike the incidence in the Before period. This asymmetry of outcomes before and after exposure onset is the focus of sequence symmetry analysis (SSA), an elegantly simple technique for hypothesis screening with large databases [6, 7]. Under the null hypothesis of no direct or indirect causal relation between exposure and outcome, incidence of outcomes is expected to be symmetric around time zero. Either the exposure or the outcome variable can be set as time zero. If we did a SSA with the outcome date set as time zero, it would look exactly like *Figure 1b*. Note that the pattern of vaccinations in *Figure 1b* is not only asymmetric; it is an exact mirror image of the pattern of outcomes in *Figure 2*.

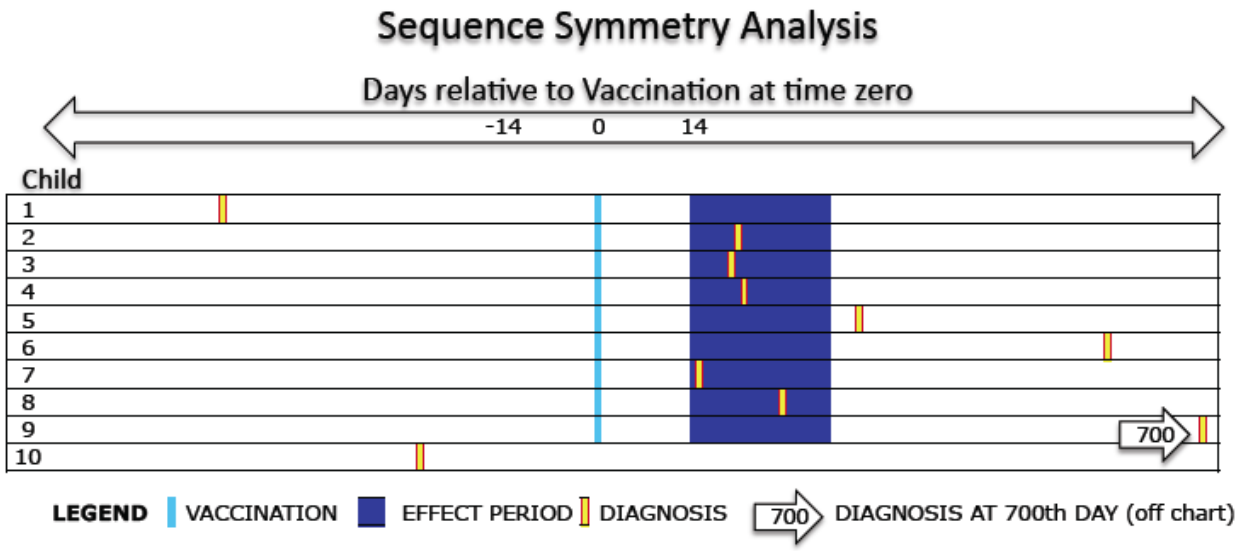


**Figure 2.** Time scale of sequence symmetry analysis with vaccination time set as zero, using data on measles-mumps-rubella vaccination and viral meningitis from Whitaker HJ et al. Tutorial in biostatistics: the self-controlled case series method. *Statistics in Medicine* 2006;25:1768-97.

The arrows in *Figure 2*, labeled Before and After, indicate the meaning of the term *bidirectional.* A bidirectional design includes time before and after the index time. In *Figure 2*, the Before period is the unexposed control time; the After period is exposed. The corresponding single arrow in *Figure 1b* indicates that the standard CCO is a *unidirectional* design, which looks at exposure frequency only retrospectively from the time of the outcome. The corresponding double-headed arrow in *Figure 1a* indicates that the standard SCCS is bidirectional. Of course, exposed time (the dark blue effect period) occurs only after vaccination, but the SCCS includes unexposed control time from both before and after vaccination.

## 2. The main strength of case-based designs: self-controlled comparisons eliminate between-person confounding.

The fundamental commonality of the three designs is that analyses are conditioned on the individual (i.e. one person per stratum) yielding only within-person comparisons. This is a major strength for conducting evaluations in Mini-Sentinel because we are concerned about potential selection bias or confounding by factors not recorded in healthcare databases. By structuring the comparisons so that each person serves as their own control, we eliminate confounding and selection bias by constant (*time-invariant*) characteristics, such as chronic regular use of non-prescription drugs, average physical activity, long-term diet, alcohol drinking pattern, habitual health behaviors, tendency to seek professional care ('medicalization'), long-past health events such as illnesses, vaccinations and injuries, occupation, social support, ethnicity, smoking history and body mass history.

Of course, a second commonality is that subjects are restricted to cases. This can be regarded either as the primary characteristic that *causes* us to use a self-controlled analysis, or as a secondary *consequence* of having only one person per stratum. Reasons for preferring to study only cases include: a) with fewer subjects and fewer data on time-invariant variables, case-based designs help protect data privacy and are computationally efficient, and b) sometimes signal refinement requires additional data collection from charts to rule out potential biases. Compared to nested case-control studies, case-based designs

would require data collection from only cases. Self-controlled analyses would follow of necessity because of the restriction to cases.

More often we will use only data available in the Mini-Sentinel Distributed Database and the restriction to cases will be a consequence of doing a self-controlled analysis to control for unmeasured factors. Accordingly, some investigators regard a case-based design as just a highly stratified analysis of cohort data. This view is illustrated by Fosbol et al [8] in reporting their study of non-steroidal anti-inflammatory drugs (NSAIDs) in relation to myocardial infarctions (MIs) and deaths in a Danish cohort of one million people followed 9 years. In their *Table 4*, the authors present results from CCO analyses (using conditional logistic regression) that have exactly the same population totals as their *Table 3* of results from cohort analyses (using Cox proportional hazards models.) A benefit of this approach is to reduce the reader's potential confusion by holding the overall context of the analysis constant. But the reassurance is potentially misleading because there *was* a shift to a different population and context – i.e. a shift to a case-only study base. It is just that the shift was *not arbitrary*. The shift occurred during the CCO analysis when the computer automatically restricted the study base to the subset of the cohort who had both an outcome event and crossed between levels of exposure or covariates.

Self-matching results in strata of three types: 1) individuals always exposed, 2) individuals never exposed, and 3) individuals sometimes exposed and sometimes not, i.e. who 'cross over.' Types 1 and 2 (called *concordant* subjects in CCO literature) automatically drop out of the univariate estimation of the relative risk. Thus, merely by deciding to do a highly stratified *univariate* analysis, we are left with Type 3, a subgroup analysis comprising only individuals who cross between exposed and unexposed time, as in a crossover experiment. This is a third commonality among the designs.

In *multivariate* analyses, exposure-concordant subjects are retained if they cross between levels of other factors. For example, referring to *Figure 1a*, Whitaker et al. included Child 10 in their bivariate analysis because Child 10 did cross between levels of their binary variable for age (less than versus greater than 547 days.)

Both the SCCS and CCO analyses are influenced by the same assumptions about the lengths of the induction period and effect period (the difference between the maximum and minimum induction times in the population.) This can be seen from Child 5 and Child 7. Child 5's meningitis was diagnosed 5 days after the effect period ended. If the authors had chosen a 4-week rather than a 3-week effect period, Child 5's diagnosis would have fallen within that period in both the SCCS and CCO analyses. Child 7's meningitis was diagnosed on the second day of the effect period. If the authors had chosen a 3-week rather than a 2-week induction period, Child 7's diagnosis would have fallen outside the effect period in both the SCCS and CCO analyses.

As a result of these similarities among case-based designs, they all apply better to the study of transient effects of point or brief exposures on the immediate risk of illnesses with abrupt onset, rather than to cumulative effects of long exposures or illness with gradual onset. They all estimate only the *within-person transient effect* of an exposure event, controlling for any cumulative effect of previous chronic exposure to the same agent (where cumulative effect is defined as any effect of past exposure on the background level of risk in the unexposed times in the window of observation in the case-based study.) For Mini-Sentinel, the distinction between an adverse event caused by a transient effect of exposure and the same adverse event caused by a chronic cumulative effect of the same exposure, can be of great importance, especially in the rare situation that the transient and cumulative effects are in different directions. For example, a case-based design could yield a relative risk greater than 1, while a

cohort design yielded a relative risk less than 1 if the cumulative protective effect were greater than the transient effect (e.g., exertion and possibly alcohol consumption can trigger an MI, yet both taken chronically are believed to reduce the risk of MI in the long term.) Both relative risk estimates could be correct because they might measure different biological effects or they test different operational hypotheses [9] related to a common biological effect.

## 3. The main difference among case-based designs: directionality and its relation to within-person confounding.

### *a. Unidirectional designs reduce reverse-causality bias.*

Standard CCO studies are unidirectional, right-censored at outcome to avoid, or reduce, *reverse*-causality [10], called event-dependent exposure in SCCS literature [2]. A mild form of reverse-causality is quite common in drug safety studies: it is an indirect causal connection between the outcome and subsequent exposure, due to the tendency for outcome-related care (especially hospitalization) to involve review of all the patient's drugs, resulting in some being stopped, possibly just to 'make room' for new drugs added. A more serious form is when the outcome directly causes stopping because it is a contraindication. For example, a CCO study of cholinesterase inhibitors (CIs) and risk of hospitalization for bradycardia (a known effect of these drugs), observed 43% of users discontinued CIs after discharge from hospital [11]. By excluding person-time after the outcome, CCOs eliminate a major opportunity for reverse-causality. However, they do not eliminate reverse-causality biases that occur before the measured outcome event (e.g., hospitalization), such as within-person protopathic bias and confounding by indication (or contraindication) wherein prodromal signs of the outcome cause (or prevent) initial use of a medical product [12].

A standard SCCS study of the same database on CIs and bradycardia hospitalizations would have included post-hospitalization time in assessing each patient's total time exposed and unexposed, which would have biased the relative risk estimate upwards. Sometimes reverse-causality has only a transient effect (e.g., contraindications of vaccination), in which case a bidirectional SCCS design can be used that excludes a hypothesized interval after the outcome [2]. But reverse-causality between outcomes and drugs can be prolonged: after hospitalization for bradycardia, prescribing of CIs to some patients would cease permanently.

The most extreme form of reverse-causality bias is when death eliminates the patient's future opportunity for all exposures. A specific type of this bias has been aptly named *immortal-time bias* [13]. It occurs when a cohort is defined in the middle of the follow-up, as happens in both the standard SCCS and SSA. To enter the cohort, one must have survived the period before exposure onset. This forbids death in the Before period but not in the After period. For example, if the outcome in *Figure 1* were death, Child 1 would not have survived to be vaccinated. Like Child 10, Child 1 would contribute nothing to a univariate analysis of the effect of vaccination; the estimate would be biased upwards by underestimating prior mortality.

Two ways to deal with immortal time bias are a) to exclude deaths also from the After period (in which case, the *standard* SCCS and SSA cannot be used to study fatal outcomes) or b) to include deaths in the Before period, which can be done only if they belong to a group that clearly would have been exposed if they had survived (e.g., vaccinations at a certain age when almost every child is vaccinated.) Recently Farrington et al.[3] proposed a unidirectional version of the SCCS, suited to the study of fatal outcomes and less susceptible to reverse-causality. The person-time is left-censored at first usage of the medical

product; in other words, cases are excluded if outcomes precede first usage. Counterfactual future exposures after death are inferred by extrapolation of past exposure patterns. This unidirectional SCCS design is slightly susceptible to bias from a population-wide trend in outcomes, because the first interval is always exposed. But outcome trends are much smaller and less problematic than population-wide trends in exposure to new medical products, which affects unidirectional CCOs. In another paper in this Supplement [14], a right-censored SCCS analysis is considered, in addition to the strengths of multivariate SCCS which can control for time-varying (within-person) confounders and modifiers.

***b. Bidirectional designs reduce exposure-trend bias***

Unidirectional CCOs are susceptible to *exposure-trend bias* because the control-window always precedes the case-window [15, 16]. If exposure to a medical product is growing rapidly in the source population, the case-window will be more exposed than the control-window, especially if those windows are long or far apart. Initially, when Mini-Sentinel is conducting surveillance of a new medical product, exposure-trend bias could be a major concern. If the new medical product is used chronically (persistently without interruption) by most patients, then in the initial period of follow-up of an inception cohort, the only discordant subjects in a unidirectional CCO would be starters (the discordant exposed.) To be a discordant unexposed subject, a person would need to be a previous user who stopped, and initially these would be few if usage were continuous. This temporary shortage of discordant-unexposed patients would mean the initial discordant pair ratio (an estimate of the relative risk) would be spuriously very high. It would approach the true relative risk as the population approaches a steady state of starting and stopping. A steady state is reached almost immediately if the new medical product is used only briefly, e.g., a vaccine.

A bidirectional CCO was first developed to deal with exposure-trend bias in studies of the health effects of air pollution [17], a setting where there is no possibility of reverse-causality: air pollution levels are not affected by rates of hospitalization. A bidirectional CCO includes control windows after the outcome so that, if control windows are sampled symmetrically from the left and right of meningitis in *Figure 1b*, a linear background trend in exposure cancels out. In air pollution studies, effects on fatal outcomes still can be studied because, while a patient's death eliminates their *individual* future exposure, it does not affect the *population's* future exposure to air pollution, which is an *ecological* or *group-wide exposure*. An analogous ecological exposure in pharmacoepidemiology would be a population-wide change in exposure such as a policy of vaccinating essentially all children at a certain age or a change in drug insurance policy. Bidirectional CCOs of fatal outcomes would work in these situations. SCCS and SSA should also work as long as they used dynamic cohorts that allowed people to die in the before period as well as the after period.

Another way to deal with exposure-trend bias is the *case-time-control design* [15]. It is a unidirectional CCO plus a unidirectional time-matched non-case group (i.e. a traditional matched control group sampled from the population that produced the cases.) Exposure odds ratios (OR) are calculated the same way in the case group and the non-case control group, and the latter's OR is considered an estimate of the exposure-trend bias in the former's OR. Dividing the case OR by the control OR gives an adjusted OR that is relatively free from exposure-trend bias. In response to the concern that non-cases might have different exposure trends than cases [16], the case-time-control design has been adapted using future cases as present controls, an adaptation called the *case-case-time-control design* [18].

### 4. Case-based designs complement cohort designs, but analyzing intermittent users requires accurate data on exposure timing

The first reason that case-based designs complement cohort designs is because intermittent users complement continuous users and continuous non-users, together comprising the whole population. Continuous users and non-users are the purest subgroups from the standpoint of an investigator of a cohort study, whereas the intermittent users are problematic, like patients who do not adhere to protocol in a randomized controlled trial. In contrast, an investigator of a case-based self-controlled design is interested in intermittent users more than continuous users and non-users.

A second reason, particularly in regards to Mini-Sentinel's Distributed Database, is that the biases in studying intermittent users complement the biases in studying continuous users. We have seen that intermittent users enable self-controlled designs that eliminate time-invariant confounding. But this often comes at a price: greater potential for bias from exposure misclassification when dispensing date in healthcare databases is not a good measure of the timing of self-administration. Another source of greater susceptibility to exposure misclassification occurs when using the discordant-pair ratio to estimate the OR: error in one of the paired observations robs information from the other observation, as the now concordant pair drops out [19]. Continuous users enable better exposure classification, but the price is greater potential bias due to unmeasured confounders and selection factors. Among intermittent users, the degree of exposure misclassification, of course, depends on the nature of the medical product. *Table 1* lists medical products that have been studied by case-based designs, ranked approximately by their brevity of use and effect periods, and the accuracy of data on exposure timing.

**Table 1.** Case-based studies grouped by types of medical products and adverse events, ranked approximately by decreasing accuracy of timing of exposure and increasing duration of windows of observation (hypothesized effect periods). SCCS = self-controlled case series. CCO = case-crossover design. CTC = case-time-control design. SSA = sequence symmetry analysis.

| Medical product | Windows (days) | Adverse Events | Design | Reference |
|---|---|---|---|---|
| ***A. Professionally Administered*** | | | | |
| ***1. Vaccine*** | | | | |
| Acellular pertussis vaccine, DTaP | 0, 1-3 | Seizures | SCCS | Huang [5] |
| Diphtheria-Tetanus-Pertussis (DTP) | 0-3, 0-7 | Fever and convulsions | SCCS | Ward [4] |
| Diphtheria-Tetanus-Pertussis (DTP) | 4, 7 | Convulsions | SCCS | Gold [1] |
| Diphtheria-Tetanus-Pertussis (DTP) | 6-11, 15-35 | Febrile convulsions | SCCS | Farrington [3] |
| Meningococcal C conjugate | 0-3, 4-7, 8-14 | Convulsions | SCCS | Andrews [2] |
| Meningococcal C conjugate | 3, 7 | Fever and convulsions | SCCS | Ward [4] |
| Measles-Mumps-Rubella, MMR | 6–11 | Convulsions | SCCS | Musonda [18] |
| Measles-Mumps-Rubella, MMR | 6-11,15-35 | Convulsions and encephalitis | SCCS | Ward [4] |
| Measles-Mumps-Rubella, MMR | 6-11, 15-35 | Febrile convulsions, aseptic meningitis, purpura | SCCS | Farrington [3] |
| Measles-Mumps-Rubella, MMR | 6, 21 | Febrile seizures | SCCS | Gold [1] |

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|---|---|---|---|---|
| Influenza vaccine | 2 | Asthma | SCCS | Kramarz [17] |
| DTP, DTaP, Hepatitis B or any vaccine | 1-7 | Wheezing | SCCS | Mullooly [7] |
| Influenza vaccine | 14 | Asthma exacerbation | SCCS | Farrington [14] |
| Penta- / hexavalent, multidose vaccines | 3 | Unexplained sudden unexpected death | SCCS | Kuhnert [25] |
| Oral Polio Vaccine | 3-10 | Myocardial infarction and stroke | SCCS | Smeeth [29] |
| Influenza vaccine | 1-14, 15-28, 29-59… | Acute myocardial infarction | SCCS | Gwini [15] |
| Oral Rotavirus vaccine | 3-5 | Intussusception | SCCS | Murphy [30] |
| Oral Polio Vaccine | 0-13, 14-27, 14-41 | Intussusception | SCCS | Andrews [26] |
| Oral Polio Vaccine | 0-14, 15-28, 29-42; 0-7, 8-14,15-21… | Intussusception | SCCS | Galando Sardiñas [27] |
| Oral Polio Vaccine | 3-7, 8-21, 28-41 | Intussusception | SCCS | Cameron [28] |
| Trivalent inactivated influenza | 0, 1-3, 4-7, 8-14, 15-28 | fever/chill, musculoskeletal pain, allergic, ophthalmologic, immunization-related adverse effects | SCCS | Mullooly [10] |
| | 0-7, 1-21, 1-42 | Seizures, meningoencephalitis, Bell's palsy, other cranial nerve disorders, demyelinating disease, peripheral nervous system disorders, neuropathy, ataxia, anaphylaxis, Guillian-Barré syndrome, etc. | SCCS | Green [11] |

| | | | | |
|---|---|---|---|---|
| | 0-3, 1-14, 5-42, 1-42 | Anemia, convulsions, gastritis/duodenitis, lymphadenitis, noninfectious gastroenteritis, serum reaction, sickle cell anemia, urticaria, viral enteritis | SCCS | Hambidge [13] |
| | 14 | Asthma, diabetes mellitus, sinusitis, upper respiratory tract infection, otitis media, rhinitis, bronchitis, bronchiolitis, pneumonia, dyspnea/respiratory abnormalities, dermatitis, renal and ureteral illness | CCO | France [12] |
| Parenteral inactivated influenza vaccine | 7, 14, 28 | Bell's palsy | SCCS | Musonda [18] |
| Influenza vaccine - inactive nasal form | 0-30, 31-60, 61-90 | Bell's palsy, Guillain-Barré Syndrome | SCCS | Stowe [16] |
| Influenza vaccine - inactive nasal form | 91 | Bell's palsy | SCCS | Mutsch [19] |
| Measles-Mumps-Rubella, MMR | 0-30, 31-60 | Gait disturbance | SCCS | Miller [22] |
| Measles-Mumps-Rubella, MMR | 21 | Meningitis | SCCS | Ki [20] |
| Diphtheria-Tetanus-Pertussis (DTP) | 21 | Idiopathic thrombocytopenia purpura | SCCS | Gold [1] |
| Meningococcal C conjugate | 27 | Purpura | SCCS | Andrews [2] |
| Measles-Mumps-Rubella, MMR | 42 | Purpura | SCCS | Andrews [2] |
| DTP, DTaP, Hepatitis B or any vaccine | 42 | Immune hemolytic anemia | SCCS | Naleway [6] |
| Poliovirus, Poliomyelitis, Oral | 1-2,1-3, 1-12 months | Multiple sclerosis relapse | CCO | Confavreux [8] |
| Tetanus Toxoid | 60 | Multiple sclerosis relapse | CCO | Confavreux [8] |

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|---|---|---|---|---|
| Meningitis vaccine | 30, 60, 180 | Relapse in nephrotic syndrome | SCCS | Taylor [24] |
| Measles-Mumps-Rubella, MMR | 90 | Invasive bacterial infection | SCCS | Miller [21] |
| Hepatitis B vaccine | 0-60, 61-365 | Central nervous system demyelinating events | SCCS | Hocine [9] |
| Measles-Mumps-Rubella, MMR | 1-2 years | Autism | SCCS | Taylor [22] |
| Measles-Mumps-Rubella, MMR | 5 years | Autism | SCCS | Farrington [23] |
| ***2. Devices*** | | | | |
| Colonoscope | 7-28 | Ulcerative colitis exacerbation | CCO | Menees [67] |
| ***B. Self-Administered*** | | | | |
| ***1. Antibiotics*** | | | | |
| Quinolones, sulfonamides, azoles (with warfarin) | 21-30 | Gastrointestinal bleeds | CCO | Schelleman [31] |
| Macrolides and fluoroquinolones | 28 | Ventricular Arrhythmia & Cardiac Arrest | CCO<br>CTC | Zambon [33] |
| Antibiotics | 60 | Risk of Flare of IBD | CCO | Aberra [32] |
| ***2. NSAIDs*** | | | | |
| Nonsteroidal anti-inflammatory drugs | 1, 3, 6 | Diarrhea | CCO | Etienney [38] |

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|---|---|---|---|---|
| Nonsteroidal anti-inflammatory drugs | 28 | Hepatitis | CCO | Lee [34] |
| NSAIDs, coxibs | 30 | Myocardial infarction | CCO | Fosbøl [35] |
| Nonsteroidal anti-inflammatory drugs | 30 | Myocardial infarction or Heart failure | CCO | Gislason [36] |
| NSAIDs, coxibs | 30 | Death or reinfarction | CCO | Gislason [37] |
| Nonsteroidal anti-inflammatory drugs | 30 | Stroke | CCO | Chang [40] |
| Nonsteroidal anti-inflammatory drugs | 90 | Gastrointestinal bleeds | CCO | Biskupiak [41] |
| ***3. Psychotropics*** | | | | |
| Benzodiazepines, other psychotropics | 1 | Motor vehicle accident | CCO | Barbone [44] |
| Benzodiazepines | 2 | Falls | CCO | Neutel [46] |
| Benzodiazepines | 5 | Hip fracture | CCO | Hoffmann [47] |
| Benzodiazepines | 7 | Motor vehicle crashes | CCO | Hébert [42] |
| Zolpidem | 7, 8-14,15-21,22-28 | Motor vehicle accident | CCO | Yang [43] |
| Psychotropics | 28 | Motor vehicle accident | SCCS | Gibson [45] |
| Tricyclic and SSRI antidepressants | 7, 8-14,15-21,22-28 | Myocardial infarction | SCCS | Tata [52] |
| SSRI antidepressants | ? | Gastrointestinal bleeds | CCS | Dall [53] |

| | | | | |
|---|---|---|---|---|
| Antipsychotics | 7 | Stroke | SCCS | Pratt [49] |
| Antipsychotics | 35 | Stroke | SCCS | Douglas [50] |
| Bupropion | 28 | Sudden death | SCCS | Hubbard [48] |
| Cholinesterase inhibitors | 90 | Bradycardia | CCO | Park-Wyllie [51] |
| ***4. Cardiovascular*** | | | | |
| Statin | 180 | Myopathy, myalgia | CCO | Molokhia [54] |
| Antihypertensives | 33 mo | Depression (initiation of antidepressant) | SSA | Hallas [56] |
| Angiotensin-converting enzyme inhibitors | 10 y (?) | Lupus exacerbation | CCO | Duran-Barragan [57] |
| ***5. Miscellaneous*** | | | | |
| Acitretin | 20, 120 | Vulvo-vaginal candidiasis | CCO | Sturkenboom [61] |
| Inhaled tiotropium bromide | 30 | Stroke | SCCS | Grosso [58] |
| Chinese herbs (prescribed) | 30, 60 | Hepatitis | CCO | Lee [65] |
| Ephedrine, caffeine | 90 | Cardiovascular events | CCO | Hallas [55] |
| Many drugs | 30, 60, 90, 120 | Central nervous system events (delirium) | CCO | Wang [59] |

| | | | | |
|---|---|---|---|---|
| Many drugs | 60 | Birth defects | CCO CTC | Hernández-Díaz [60] |
| Many drugs | 90 | Psoriasis vulgaris hospitalizations | CCO | Cohen [39] |
| Isotretinoin | 150 | Antidepressant prescription | CCO | Azoulay [63] |
| Isotretinoin | 365 | Antidepressant prescription | CCO | Hersom [62] |

Vaccines and episodic use of medical devices (e.g., colonoscopy) are ranked at the top of *Table 1* because the exposures are brief and infrequent, and their timing is well documented by the health professionals who administer them. Therefore, exposure misclassification is relatively low. (Exposure misclassification in vaccine studies arise mostly in hypothesizing the lengths of the induction and effect periods.) The SCCS method is particularly suited to situations when each person's time can be accurately classified as exposed or unexposed, which is why the SCCS method is routinely used both for active surveillance and retrospective studies of vaccines.

Ranked second are antibiotics because they are normally used briefly and infrequently, and the timing of use is usually immediately after dispensing. However, many people stop taking antibiotics before the full course of tablets is complete. Therefore, exposure misclassification increases with days since dispensing. Unlike vaccines, but like colonoscopy, antibiotics are usually prescribed in response to medical problems, and occasionally in anticipation of a medical event (e.g., imminent surgery). Therefore, within-person confounding by indication and reverse-causality bias are more likely in studies of antibiotics than vaccines.

Case-based studies of NSAIDs are more susceptible to exposure time misclassification than antibiotics because NSAIDs are not normally prescribed as a course; many patients take them sporadically. Immediately after dispensing, the probability of NSAID use is high, but choosing a cut-off date when usage has probably stopped is more difficult than with antibiotics. Therefore, overall relative risk estimates from case-based studies are more questionable for NSAIDs than for antibiotics.

The more uncertainty there is about when patients were exposed to a product, the more selective the investigator must be about what people and what times to include. For example, we can exclude sporadic users and do a case-based study restricted to people with a series of regularly spaced dates of NSAID dispensing spanning several months, preceded and followed by long periods with no dispensing of NSAIDs.

Some psychotropic medications (e.g., drugs for anxiety) are taken sporadically in response to fluctuating symptoms, so the days when the patient is exposed are mostly unknown and case-based designs are largely infeasible. Other psychotropics are taken with regularly spaced dispensing dates spanning several months which are preceded and followed by long periods with no dispensing. Then case-based designs are feasible.

Many cardiovascular medications are prescribed as lifelong therapies and would not be amendable to case-based designs if all patients were adherent. However, stoppers are common enough that case-based designs have proven to be possible, although the reason for stopping might an unmeasured contraindication.

The more selective we are about subsets of *people* to include, the more selective we are inclined to be about subsets of *times* to include. Consequently, as we move down *Table 1* and exposure timing becomes more inaccurate, the more attractive are matched CCO designs. It makes increasing sense to use the outcome as time zero and inspect the patterns of exposure data in a case window and a matching control window. Also inspecting data for potential within-person confounding by factors that coincide with both the outcome and the immediately preceding exposure event, is probably easier to do when the outcome event is chosen as time zero. By analogy, within-person confounders would probably be easier to visualize in *Figure 1b* than in *Figure 1a* simply because of the way the data are aligned.

One message from *Table 1* is that SCCS and CCO designs are complementary. SCCS tends to be preferable at the top of the table and CCO tends to become preferable as we move down. There is no obvious cut-off point. In the middle, some investigators (whom we might call 'lumpers') would prefer to keep all the observation time in the analysis and deal with threats to validity by including additional terms in statistical models, as in SCCS designs. Other investigators (whom we might call 'splitters') would prefer to handle threats to validity by restriction/selection, as in CCO designs. Other factors that played no role in *Table 1* rankings, e.g., time-varying confounding, would also influence instigators' preferences.

The further down *Table 1* we go, the more chronic users there are in the population and the more we regard cohort designs as primary, and case-based designs as secondary. Also, the further down we go, the more we rely on head-to-head comparisons, which in case-based designs entails examining multiple medications in relation to one class of outcome. In reviewing these studies, we repeatedly found that comparing relative risks for different drugs, particularly similar active comparators or 'negative control' drugs that are expected to have no effect, was helpful for assessing potential biases. Therefore, Mini-Sentinel should anticipate investigators wanting to evaluate multiple comparator products as controls in case-based studies that are primarily intended to evaluate a single medical product.

## B. MULTIVARIATE SELF-CONTROLLED CASE SERIES

Farrington[1] proposed the self-controlled case series (SCCS) method in order to estimate the relative incidence of adverse events to assess vaccine safety. The major features of SCCS are that (1) it automatically controls for fixed individual baseline covariates, and (2) only cases (individuals with at least one event) need to be included in the analysis. With SCCS, each individual serves as their own control.

SCCS is one of several self-controlled methods that the epidemiology literature describes, many of which are variants on the case-crossover method[4]. However unlike the case-crossover method, which requires the choice of a comparator time period to serve as a control, SCCS makes use of all available temporal information without the need for selection.

The standard SCCS model considers one AE and one drug of interest. However patients generally take multiple drugs throughout the course of their observation period. Additionally, patients may take many different drugs at the same time point, which leads to a potential for drug interaction effects. In order to account for the presence of multiple drugs and interactions, the intensity expression for the SCCS model can be extended in a natural way. Farrington's original SCCS approach considered other time-varying covariates such as age and the multivariate SCCS (MSCCS) builds on his work. We refer the reader to [83] and Appendix 2 for a detailed description.

The set of figures below demonstrate the empirical performance of the MSCCS method in the context of the OMOP HOI experiment. This experiment considers 53 drug-outcome pairs, 9 of which are known to be positively associated. *Figure 1* shows that MSCCS outperforms its univariate counterpart (USCCS) on all four databases and is amongst the top methods presented. *Figure 2* presents the same information but grouped by database. *Figure 3* shows the actual Receiver-Operating Characteristic (ROC) curves for USCCS and MSCCS and makes visually apparent the improvement in area-under-the-curve presented in *Figure 1*. Each dot in each panel of *Figure 3* represents the sensitivity-specificity tradeoff that can be achieved with different choices of threshold for the observed relative risk. Ideally, each panel would have a point in the upper left corner corresponding to high sensitivity and high specificity. While MSCCS

does have points closer to the upper left corner than USCCS, considerable room for improvement still exists.

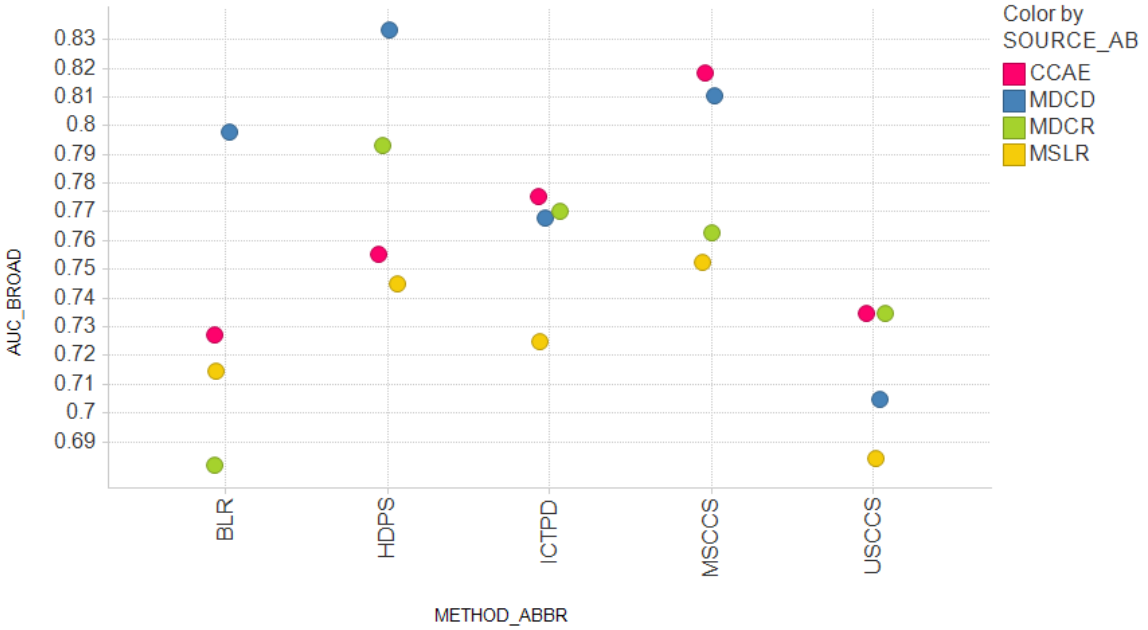


**Figure 1.** Performance of MSCCS as compared with univariate SCCS (USCCS) and three other methods, BLR (Bayesian Logistic Regression), HDPS (High-dimensional Propensity Scoring) and ICTPD (Information Component Temporal Pattern Discovery). The vertical axis show area-under-the-curve in the OMOP HOI experiment. CCAE, MDCD, MDCR, and MSLR are four different claims databases.

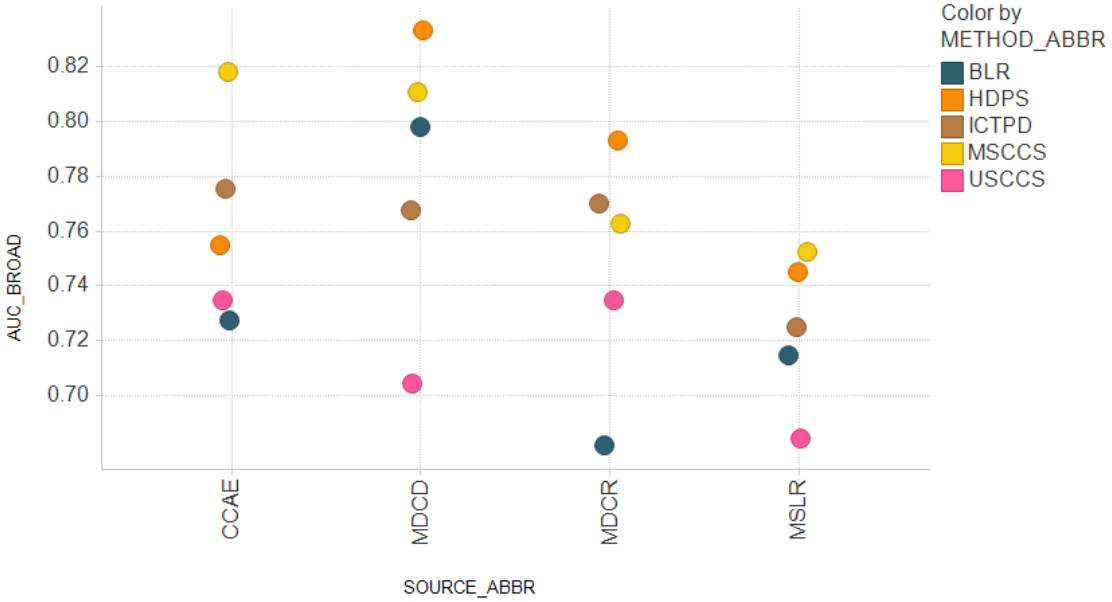


**Figure 2.** Performance of MSCCS as compared with univariate SCCS (USCCS) and three other methods, BLR (Bayesian Logistic Regression), HDPS (High-dimensional Propensity Scoring) and ICTPD (Information Component

Temporal Pattern Discovery). The vertical axis show area-under-the-curve in the OMOP HOI experiment. CCAE, MDCD, MDCR, and MSLR are four different claims databases.

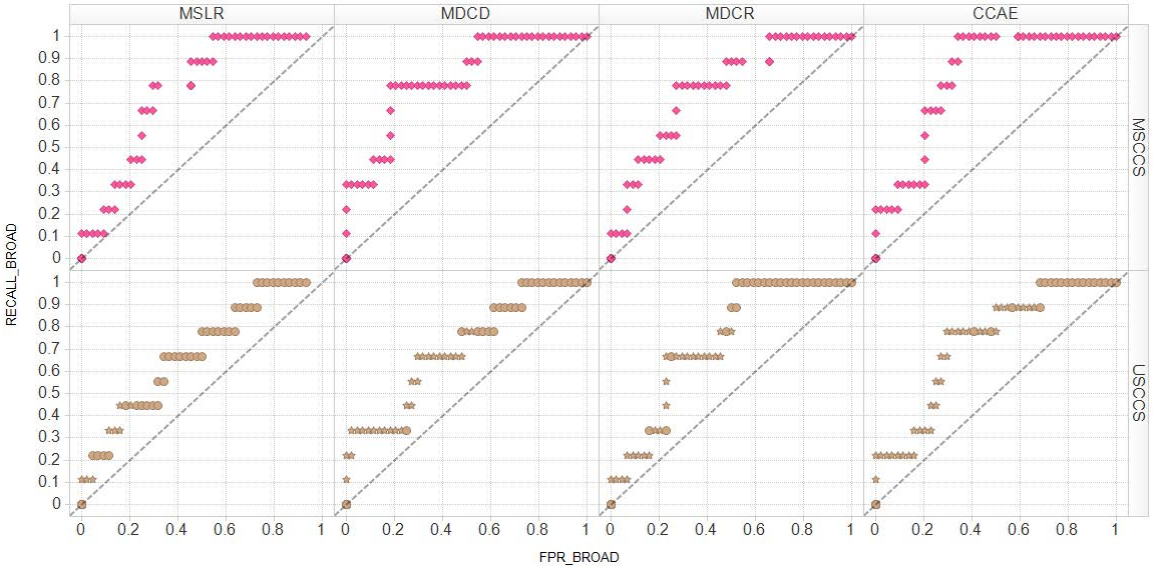


**Figure 3.** Receiver-Operator Characteristic curves to illustrate performance of multivariate self-controlled case series (MSCCS) as compared with univariate SCCS (USCCS) on four databases. Each column represents a different claims database. The first row represents MSCCS and the second row represents USCCS. Within each panel, the horizontal axis sows the false positive rate and the vertical axis shows sensitivity. Each dot represents one of the 53 drug-outcome pairs in the OMOP HOI experiment.

### SCCS versus Case-crossover

The group also empirically compared the self-controlled case series approach with the case-crossover (CCO) approach in the context of the OMOP experiment. *Figure 4* below presents the findings graphically. Each dot represents a drug-outcome pair, and the red line segments represent 95% intervals (CCO on the horizontal axis and SCCS on the vertical axis). Many drug-outcome pairs lie close to the diagonal in *Figure 4*, and thus for these pairs, SCCS and CCO essentially agree. However, there are drug-outcome pairs where sharp disagreement exists between the two methods. For example, for antiepileptics and angioedema (bottom right in *Figure 4*), CCO produces a log relative risk of about 1.5 (corresponding to a relative risk of 4.5) while SCCS produces a log relative risk of about -0.5 (corresponding to a relative risk of 0.6). However, for this pair, and for many of the off-diagonal pairs, the 95% confidence intervals for both estimates overlap substantially.

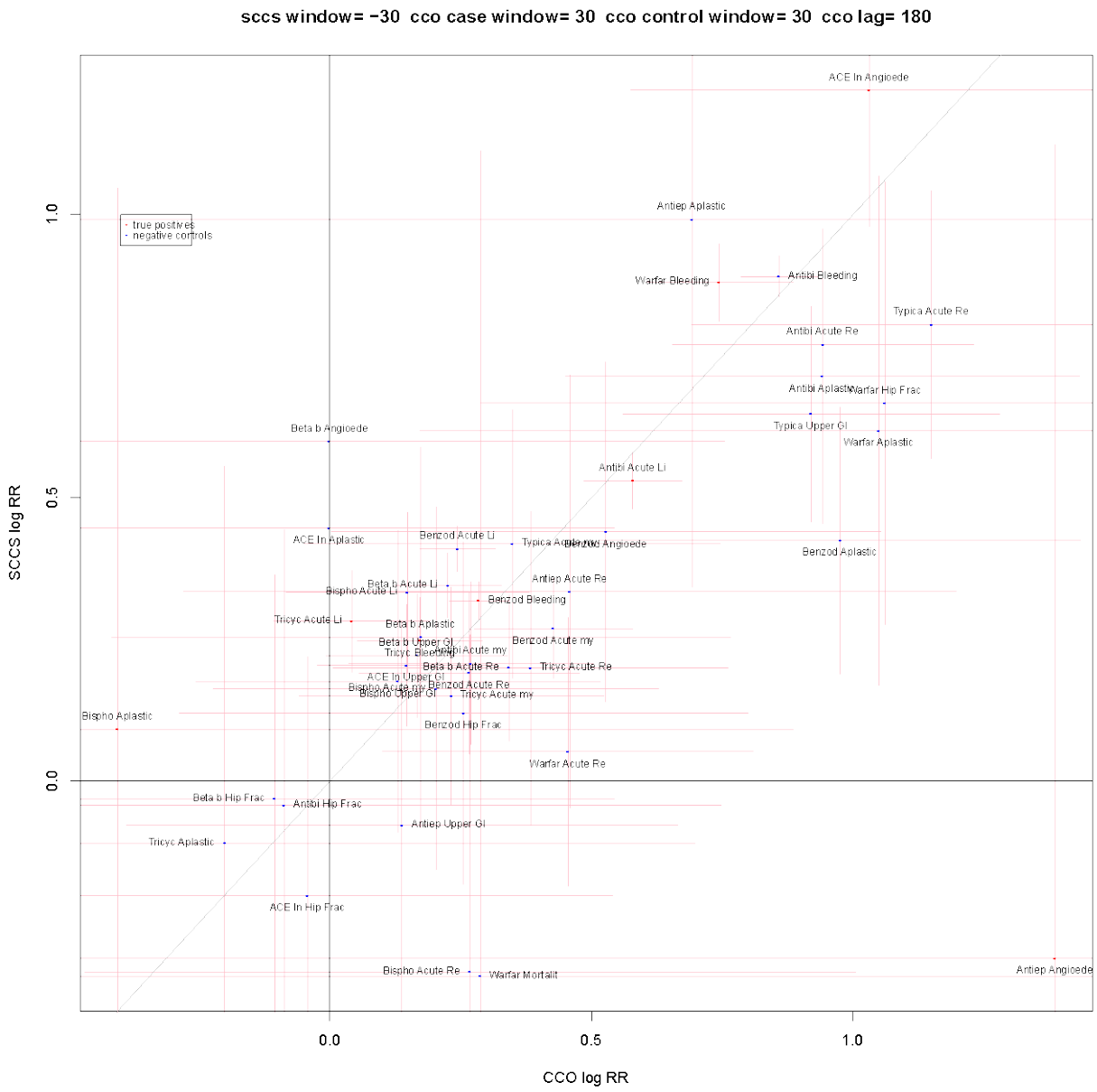


**Figure 4.** Point estimates (red and blue dots) and 95% confidence intervals for SCCS versus case-crossover methods. The red dots represent true positive pairs and the blue dots are negative controls. The numbers at the top of the figure represent method-specific parameter choices in days.

## C. RECOMMENDATIONS TO MINI-SENTINEL

- Case-based methods are useful insofar as they provide an alternative approach to confounding control.

- Case-based designs can be superior to cohort designs for signal refinement when the medical product is used only briefly on or after a well-recorded date (e.g., vaccine, antibiotic) and when

unmeasured time-invariant characteristics of the patients are suspected of being confounders or selection factors in a cohort analysis.

- Case based designs are problematic when dispensing dates are not a good measure of the time of self-administration and when dates of medically-attended events are not good measures of the onset of the underlying outcomes of interest. For example if the condition has a variable and insidious onset - like many cancers - that are unmeasured until we see a diagnosis at a visit or hospital stay.

- Case-based studies of intermittent users often complement cohort studies of continuous users, but are only as representative as the subgroup of intermittent users. As with any subgroup analysis, we often will not know, until we are immersed in our data, what are the main threats to validity and the relative merits of case-based versus cohort methods.

- Bidirectional SCCS and unidirectional CCOs are complementary because they have different susceptibility to reverse-causality bias and exposure-trend bias. Both of these biases pose challenges for signal refinement in surveillance of new medical products. Modifications of both designs deal with these biases in some situations. Continued research is needed comparing the performance of these designs.

- SSA might be an efficient tool for signal generation in future but would be counterproductive before Mini-Sentinel has established methods for signal refinement.

- Mini-Sentinel should capture bidirectional outcome data before starting and after stopping use of medical products. If the logistics of Mini-Sentinel data management dictate that follow-up starts no earlier than first use of the medical product, a left-censored SCCS design is possible if enough patients stop and provide post-exposure outcome data.

- Case-based approaches require fewer patient records and fewer variables (little or no data on time-invariant characteristics), so they are computationally efficient and suited to Mini-Sentinel's aim to preserve privacy.

- There is no free lunch – the underlying assumptions for case-based approaches may or may not be reasonable in practice.

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# III. THE SELF-CONTROLLED CASE SERIES: RECENT DEVELOPMENTS

## A. OVERVIEW

Increasing scientific, regulatory and public scrutiny focuses on the obligation of the medical community, pharmaceutical industry and health authorities to ensure that marketed medical products have acceptable benefit-risk profiles. This is an intricate and ongoing process that begins with carefully designed randomized clinical trials prior to approval but continues after regulatory market authorization when the product is in widespread clinical use. In the post-approval environment, surveillance schemes based on spontaneous reporting systems (SRS) represent a cornerstone for the early detection of novel medical product hazards. Key limitations of SRS-based pharmacovigilance include under-reporting, duplicate reporting, and the absence of a denominator or control group to provide a comparison.

Newer data sources have emerged that overcome some of the SRS limitations but present methodological and logistical challenges of their own. Longitudinal observational databases (LODs) provide time-stamped patient-level medical information, such as periods of medical product exposure and dates of diagnoses. Typical examples include medical claims databases and electronic health record systems. The scale of some of these databases presents interesting computational challenges – the larger claims databases contain upwards of 50 million lives with up to 10 years of data per life. A nascent literature on risk identification and refinement in LODs now exists including adaptations of some of the Bayesian methods developed in the SRS context.

In this paper we consider one particular approach, the self-controlled case series. We present a Bayesian analysis of this method and provide an overview of some recent related developments. We use the term "drug" in what follows but our comments pertain to medical products more generally.

## B. LONGITUDINAL OBSERVATIONAL DATABASES

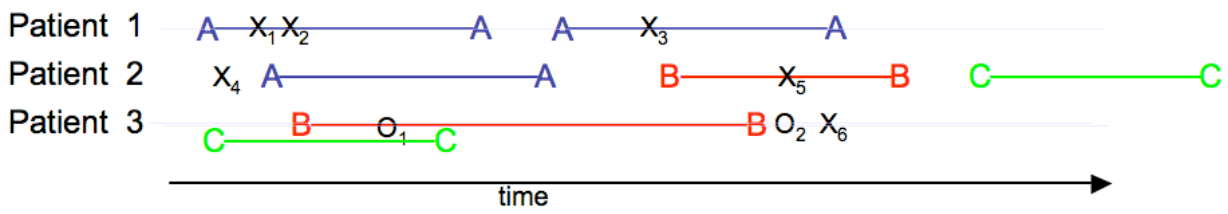


**Figure 1.** A longitudinal observational dataset with three patients, three distinct drugs (A, B, and C) and two distinct outcome events (X and O)

*Figure 1* provides a schematic of LOD data for coverage periods for three patients. Patient 1 was exposed to drug A during two separate exposure periods. While on drug A, patient 1 experienced outcome event X on three different occasions. Patient 2 was exposed to drugs A, B, and C during successive non-overlapping eras. Patient 2 experienced outcome event X before consuming any drugs and also experienced outcome event X while consuming drug B. Patient 3 was exposed to drug C and later started taking drug B in addition to drug C. This patient experienced outcome event O while taking both B and C and later experienced outcome events O and X after the drug B and C eras had ended. We note that LODs generally provide drug prescription dates so that construction of drug "eras" involves subtle decisions concerning gaps between successive prescriptions as well as off-drug risk periods. With

outcome events, we think of outcomes as occurring at points in time whereas in truth outcomes are processes spread out in time.

The methodological challenge is to estimate the strength of the association between each drug and each outcome event, while appropriately accounting for covariates such as other drugs and outcome events, patient demographics, etc.

In this context, several papers have looked at vaccine safety, for example, Lieu et al. (2007), McClure et al. (2008), and Walker (2009). The Vaccine Safety Datalink provides an early example of a LOD specifically designed for safety. Papers focusing on drug safety include Curtis et al. (2008), Jin et al. (2008), Kulldorff et al. (2008), Li (2009), Noren et al. (2008), and Schneeweiss et al. (2009).

## C. THE SELF-CONTROLLED CASE SERIES METHOD

Farrington (1995) proposed the *self-controlled case series* (SCCS) method in order to estimate the relative incidence of adverse events to assess vaccine safety. The major features of SCCS are that (1) it automatically controls for time-fixed covariates that don't vary within a person during the study period, and (2) only cases (individuals with at least one event) need to be included in the analysis. With SCCS, each individual serves as their own control. In other words, SCCS compares outcome event rates during times when a person is exposed versus outcome event rates during times when the same person is unexposed. In effect, the cases' unexposed time lets us infer expectations about what would have happened during their exposed time had they not been exposed.

SCCS is one of several self-controlled methods that the epidemiology literature describes, many of which are variants on the case-crossover method (Maclure, 1991). However unlike the case-crossover method, which typically requires the choice of a comparator time period to serve as a control, SCCS makes use of all available temporal information without the need for selection.

Epidemiological applications of SCCS tend to focus on situations with small sample sizes and few exposure variables of interest. In contrast, the problem of drug safety surveillance in LODs must contend with millions of individuals and millions of potential drug exposures. The size of the problem presents a major computational challenge – ensuring the availability of an efficient optimization procedure is essential for a feasible implementation.

### 1. One drug, one adverse event

We will first focus on the case where there is one drug and one adverse event of interest.

To set up the notation, $i$ will index individuals from $1$ to $\mathrm{N}$. Events and exposures in our databases are recorded with dates, so temporal information is available down to the level of days (indexed by $d$). Let $\tau_i$ be the number of days that person i is observed, with $(i,d)$ being their $d$th day of observation. The number of events on day $(i,d)$ is denoted by $y_{id}$, and drug exposure is indicated by $x_{id}$, where $x_{id} = 1$ if $i$ is exposed to the drug on $(i,d)$, and $0$ otherwise.

SCCS assumes that AEs arise according to a non-homogeneous Poisson process, where the underlying event rate is modulated by drug exposure. We will start with the simple assumption that person $i$ has their own individual baseline event rate $e^{\varphi_i}$, which is constant over time. Under the SCCS model, drug

exposure yields a multiplicative effect of $e^{\beta}$ on the baseline incidence rate. In other words, the event intensity for person $i$ on day $d$ can be written as a function of drug exposure $x_{id}$.

$$\lambda_{id} = e^{\phi_i + \beta x_{id}}$$

The number of events observed on $(i,d)$ given the current exposure status is distributed as a Poisson random variable with rate $\lambda_{id}$, which has the following density:

$$P(y_{id} \mid x_{id}) = \frac{e^{-\lambda_{id}} \lambda_{id}^{y_{id}}}{y_{id}!}$$

The SCCS likelihood contribution for person $i$ is the joint probability of the observed sequence of events, conditional on the observed exposures

$$L_i^c = P(y_{i1}, \ldots, y_{i\tau_i} \mid x_{i1}, \ldots, x_{i\tau_i}) = P(\mathbf{y}_i \mid \mathbf{x}_i) = \prod_{d=1}^{\tau_i} P(y_{id} \mid x_{id})$$

There are two assumptions implicit in the Poisson model that allow us to write out this likelihood:

1. events are conditionally independent given exposures

$$y_{id} \perp\!\!\!\perp y_{id'} \mid \mathbf{x_i} \quad \text{for } d \neq d', \text{ and}$$

2. past events are conditionally independent of future exposures given the current exposure

$$y_{id} \perp\!\!\!\perp x_{id'} \mid x_{id} \quad \text{for } d \neq d'.$$

These assumptions are likely to be violated in practice (e.g., one might expect that having an MI increase the future risk of an MI and also impacts future drug usage), however they allow for simplifications in the model. At this point one could maximize the full log-likelihood over all individuals ($l^c = \Sigma_i \log L^c_i$) in order to estimate the parameters. However since our primary goal is to assess drug safety, the drug effect $\beta$ is of primary interest and the person-specific $\varphi_i$ effects are *nuisance parameters*. A further complication is that claims databases can contain well over 10 million patients. Since the dimension of the vector of person-specific parameters $\varphi = (\varphi_1, \ldots, \varphi_N)'$ is equal to the number of individuals $N$, estimation of $\varphi$ would call for optimization in an ultra high-dimensional space and presumably would be computationally prohibitive.

In order to avoid estimating the nuisance parameter, we can condition on its sufficient statistic and remove the dependence on $\varphi_i$. Under the Poisson model this sufficient statistic is the total number of events person $i$ has over their entire observation period, which we denote by $n_i = \Sigma_d y_{id}$. For a non-homogeneous Poisson process, $n_i$ is a Poisson random variable with rate parameter equal to the cumulative intensity over the observation period:

$$n_i \mid \mathbf{x}_i \sim \text{Poisson}(\sum_{d=1}^{\tau_i} \lambda_{id} = e^{\phi_i} \sum_{d=1}^{\tau_i} e^{\beta x_{id}})$$

In our case the cumulative intensity is a sum (rather than an integral) since we assume a constant intensity over each day. Conditioning on $n_i$ yields the following likelihood for person $i$:

$$L_i^c = P(\mathbf{y}_i \mid \mathbf{x_i}, n_i) = \frac{P(\mathbf{y}_i \mid \mathbf{x_i})}{P(n_i \mid \mathbf{x_i})} \propto \prod_{d=1}^{\tau_i} \left( \frac{e^{\beta x_{id}}}{\sum_{d'} e^{\beta x_{id'}}} \right)^{y_{id}}$$

Notice that because $n_i$ is sufficient, the individual likelihood in the above expression no longer contains $\varphi_i$. This conditional likelihood takes the form of a multinomial, but differs from a typical multinomial regression. Here the number of "bins" (observed days) varies by person, the $\beta$ parameter is constant across days, and the covariates $x_{id}$ vary by day.

Assuming that patients are independent, the full conditional likelihood is simply the product of the individual likelihoods.

$$L^c \propto \prod_{i=1}^{N} \prod_{d=1}^{\tau_i} \left( \frac{e^{\beta x_{id}}}{\sum_{d'} e^{\beta x_{id'}}} \right)^{y_{id}}$$

Estimation of the drug effect can now proceed by maximizing the conditional log-likelihood to obtain $\hat{\beta}_{CMLE}$. Winkelmann (2008) showed that this estimator is consistent and asymptotically Normal in the Poisson case.

It is clear from the expression for the likelihood that if person $i$ has no observed events ($\mathbf{y}_i = \mathbf{0}$), they will have a contribution of $L^c_i = 1$. Consequently, person $i$ has no effect on the estimation, and it follows that only cases ($n_i \geq 1$) need to be included in the analysis.

SCCS does a *within-person* comparison of the event rate during exposure to the event rate while unexposed, and thus the method is "self-controlled". Intuitively it follows that if $i$ has no events, they cannot provide any information about the relative rate at which they have events. That the SCCS analysis relies solely on data from cases is a substantial computational advantage – since the incidence rate of most AEs is relatively low, typical SCCS analyses will utilize only a modest fraction of the total number of patients.

## 2. Multiple drug exposures and drug interactions

So far we have discussed the scenario where there is one AE and one drug of interest. However patients generally take multiple drugs throughout the course of their observation period. Additionally, patients may take many different drugs at the same time point, which leads to a potential for drug interaction effects. In order to account for the presence of multiple drugs and interactions, the intensity expression for the SCCS model can be extended in a natural way.

Suppose that there are $p$ different drugs of interest, each with a corresponding exposure indicator $x_{idj} = 1$ if exposed to drug $j$ on day $(i,d)$; $0$ otherwise. Let $e^{\beta_j}$ be the multiplicative effect of drug $j$ on the event rate.

A multiplicative model describes the intensity for patient $i$ on day $d$:

$$\lambda_{id} = e^{\phi_i + \boldsymbol{\beta}' \mathbf{x}_{id}} = e^{\phi_i + \beta_1 x_{id1} + \cdots + \beta_p x_{idp}}$$

where $\mathbf{x}_{id} = (x_{id1}, \ldots, x_{idp})'$ and $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$.

Since $n_i$ is still sufficient for $\varphi_i$, person-specific effects will once again dropout of the likelihood upon conditioning. One can derive the expression in a similar manner to the previous case of one AE and one drug case, resulting in:

$$L_i^c = P(\mathbf{y}_i \mid n_i, \mathbf{X}_i) \propto \prod_{d=1}^{\tau_i} \left( \frac{e^{\boldsymbol{\beta}' \mathbf{x}_{id}}}{\sum_{d'} e^{\boldsymbol{\beta}' \mathbf{x}_{id'}}} \right)^{y_{id}} \quad \text{where} \quad \mathbf{X}_i = \begin{bmatrix} \mathbf{x}_{i1}' \\ \vdots \\ \mathbf{x}_{i\tau_i}' \end{bmatrix}$$

To simplify the summation in the denominator, days with the same drug exposures can be grouped together. Suppose that there are $K_i$ distinct combinations of drug exposures for person $i$. Each combination of exposures defines an exposure group, indexed by $k = 1, \ldots, K_i$.

For person $i$ and exposure group $k$, we need to know the number of events $i$ has while exposed to $k$ ($y_{ik}$) along with the length of time $i$ spends in $k$ ($l_{ik}$). For person $i$ we only require information for each of $K_i$ exposure groups, rather than for all $\tau_i$ days. This allows for coarser data and more efficient storage – since patients tend to take drugs over extended periods of time, $K_i$ is typically much smaller than $\tau_i$.

$$L^c \propto \prod_{i=1}^{N} \prod_{k=1}^{K_i} \left( \frac{e^{\boldsymbol{\beta}' \mathbf{x}_{ik}}}{\sum_{k'} l_{ik'} e^{\boldsymbol{\beta}' \mathbf{x}_{ik'}}} \right)^{y_{ik}} \quad (1)$$

SCCS can be further extended to include interactions and time-varying covariates (e.g., age groups). The intensity on $(i,d)$ including two-way drug interactions and a vector of time-varying covariates $\mathbf{z}_{id}$ can be written as

$$\lambda_{id} = e^{\phi_i + \boldsymbol{\beta}' \mathbf{x}_{id} + \sum_{r \neq s} \gamma_{rs} x_{idr} x_{ids} + \boldsymbol{\alpha}' \mathbf{z}_{id}}$$

where $\gamma$ denotes a two-way interaction between drugs $r$ and $s$.

*Remark 1.* In practice, many adverse effects can occur at most once in a given day suggesting a binary rather than Poisson model. One can show that adopting a logistic model yields an identical conditional likelihood to (1). This equivalence allows shifting to a logistic model with follow-up truncated at the outcome event, when that event is the onset of an enduring condition that permanently changes exposure propensity (see Discussion below.)

*Remark 2.* It is straightforward to show that the conditional likelihood in (1) is log-concave.

## 3. Bayesian Self-Controlled Case Series

We have now set up the full conditional likelihood for multiple drugs, so one could proceed by finding conditional maximum likelihood estimates of the drug parameter vector $\boldsymbol{\beta}$. However in the problem of drug safety surveillance in LODs there are millions of potential drug exposure predictors (tens of

thousands of drug main effects along with drug interactions). This high dimensionality leads to potential overfitting under the usual maximum likelihood approach, so regularization is necessary.

We take a Bayesian approach by putting a prior over the drug effect parameter vector and performing inference based on posterior mode estimates. There are many choices of prior distributions that shrink the parameter estimates toward zero and address overfitting. In particular, we focus on the (1) Normal prior and (2) Laplacian prior.

1. *Normal prior.* Here we shrink the estimates toward zero by putting an independent Normal prior on each of the parameter components. Taking the posterior mode estimates would be analogous to a ridge Poisson regression, placing a constraint on the $L_2$-norm of the parameter vector.

2. *Laplace prior.* Under this choice of prior a portion of the posterior mode estimates will shrink all the way to zero, and their corresponding predictors will effectively be selected out of the model. This is equivalent to a lasso Poisson regression, where there is a constraint on the $L_1$-norm of the parameter vector estimate.

Efficient algorithms exist for finding posterior modes, rendering our approach tractable even in the large-scale setting. In particular, we have adapted the cyclic-coordinate descent algorithm of Genkin et al. (2007) to the SCCS context. An open-source implementation is available at http://omop.fnih.org.

## D. EXTENSIONS TO THE BASIC SCCS MODEL

### 1. Relaxing the Independence Assumptions I: Events

Farrington and Hocine (2010) present an approach that extends SCCS to allow for within-individual event dependence. This method treats the vector of observed event times $\mathbf{t}_i = (t_{i1}, \ldots, t_{in_i})'$ for each individual $i$ as a single point in an $n_i$-dimensional region, where $n_i$ denotes the number of events experienced by individual $i$. This region is restricted to $Q_i(n_i) = \{ \mathbf{t}_i \in (a_i, b_i]^{n_i}: t_{i1} < \cdots < t_{in_i} \}$ (where $(a_i, b_i]$ denotes the observation period for individual $i$) since the components of $\mathbf{t}_i$ are ordered by time, and no event times can occur outside of the observation window $(a_i, b_i]$. Standard SCCS assumes that events are realizations of a one-dimensional Poisson process and conditions upon the observed number of events $n_i$. Under Farrington and Hocine's model, however, the event time vector $\mathbf{t}_i$ is treated as a single point arising from an $n_i$-dimensional Poisson process. In this framework, conditioning on $n_i$ is equivalent to conditioning on the occurrence of a single point in the region $Q_i(n_i)$.

If $\lambda_i(t_1, \ldots, t_{n_i} \mid \mathbf{x}_i)$ is the intensity of the $n_i$-dimensional Poisson process on $Q_i(n_i)$, the conditional likelihood of $\mathbf{t}_i$ given the occurrence of one such point in $Q_i(n_i)$ is

$$L_i^{n_i} = \frac{\lambda_i(t_{i1}, \ldots, t_{in_i} \mid \mathbf{x}_i)}{\int\limits_{Q_i(n_i)} \lambda_i(u_1, \ldots, u_{n_i} \mid \mathbf{x}_i) du_1 \cdots du_{n_i}} \quad (2)$$

Farrington and Hocine assume that the $n_i$-dimensional Poisson intensity can be written in the form

$$\lambda_i(t_1, \ldots, t_{n_i} \mid \mathbf{x}_i) = \prod_{j=1}^{n_i} \lambda_i(t_j \mid \mathbf{x}_i) \times H_{n_i}(t_1, \ldots, t_{n_i}) \quad (3)$$

where the product term is made up of independent univariate intensities $\lambda_i(t \mid \mathbf{x}_i)$, and the $H_{ni}$ (.) function determines the dependence between events. From (2) and (3) we can see that terms of $\lambda_i(t \mid \mathbf{x}_i)$ that are fixed in time will cancel out of the conditional likelihood, as they do in the original SCCS

model. Similarly, fixed terms of $H_{ni}$ (.) will also drop out of the conditional likelihood. Farrington and Hoccine explore different possible choices for $H$.

## 2. Relaxing the Independence Assumptions II: The PD Model

The PD-SCCS model (Simpson, 2011) extends SCCS to allow positive dependence between events, meaning that the occurrence of an event can increase an individual's future event risk. Let $N_i(t)$ record the number of events that person $i$ has experienced up until time $t$. Assume, as before, that $i$ has $n_i$ total events during their observation period and that these events occur at times $t_{i1} < \cdots < t_{ini}$. It is convenient to define a counting process, such as $N_i(t)$, in terms of its intensity function $\lambda_i(t \mid \mathbf{x}_i(t))$. This function gives the instantaneous probability that an event occurs at time $t$, given the history of the process and covariates. Under the SCCS model, the Poisson intensity for $i$ at time $t$ is

$$\lambda_i(t \mid \mathbf{x}_i(t)) = e^{\phi_i + \boldsymbol{\beta}' \mathbf{x}_i(t)} \quad (4)$$

as was previously described. PD-SCCS extends this model by incorporating $N_i(t^-)$, the number of events that $i$ has experienced up to but not including time $t$, as an additive effect on the individual baseline $e^{\varphi_i}$. The PD-SCCS intensity function takes the form

$$\lambda_i(t \mid \mathbf{x}_i(t)) = \left(e^{\phi_i} + \delta N_i(t^-)\right) e^{\boldsymbol{\beta}' \mathbf{x}_i(t)} \quad (5)$$

where $\delta$ is the parameter that controls the level of dependence between events. Based on plugging the PD-SCCS intensity (5) into the likelihood expression for a general intensity-based process, one can see that the total number of events $n_i$ is sufficient for the nuisance parameter $\varphi_i$. As in the SCCS model, conditioning on $n_i$ removes $\varphi_i$ from the likelihood expression. Symmetry arguments yield a closed form for the conditional likelihood, which in the denominator requires integrating over all possible ways for $i$ to have $n_i$ events during their observation period. Inference for $\boldsymbol{\beta}$ and $\delta$ is based on this conditional likelihood. Since the intensity function must be non-negative, the event dependence parameter is restricted to $\delta > 0$. In the case that $\delta = 0$, the PD-SCCS intensity model in (5) reduces to that of the SCCS model in (4).

## 3. Relaxing the Independence Assumptions III: Exposures

As discussed above, the SCCS model assumes that events are conditionally independent of subsequent exposures. Farrington et al. (2009) present an ingenious relaxation of this assumption using a counterfactual modeling approach. Their approach applies to the specific situation where the risk returns to its baseline level at the end of each risk period, where the event of interest is non-recurrent, and where the occurrence of the event precludes future exposures.

Here we sketch the Farrington et al. approach using a simplified version of their running example. Consider a situation in which each individual can have up to two exposures. For individual $i$, again denote by $(a_i, b_i]$ the observation period and denote by $c_{i1}$ and $c_{i2}$ the actual exposure times, should they occur.

For notational simplicity, we consider point exposures followed by some known increased-risk time. The exposures then partition the observation period into up to five periods indexed by $j$: a control period, followed by an increased-risk period, followed by a control period, followed by a second increased-risk period, followed by a final control period. Denote by $n_{ij}$ the number of events occurring in the $j$th period, $n_{ij} \in \{0, 1\}$. Let $\beta_1$ and $\beta_2$ denote the log relative incidences associated with the first and second increased risk periods respectively and denote by $T_i$ the event time.

If $T_i$ occurs after $c_{i2}$ then no further exposures can occur and inference about $\beta_2$ can proceed in the usual fashion. Inference for $\beta_1$ is more complex in the situation where the event occurs after just one exposure because the timing of the counterfactual second exposure is then unavailable. Farrington et al. then make the following key observation: suppose, counterfactually, that no individual experienced a second exposure. Then it would be possible to estimate $\beta_1$ without bias. For this to work, we would need to know $n^*_{i4}$, the number of events in the fourth period, had no second exposure occurred. This is missing for those individuals that did in fact have a second exposure. However, $n_{i4}e^{-\beta 2}$ is an unbiased estimate of $n^*_{i4}$ for these individuals – this amounts to backing out the actual elevated risk during the second exposure. Using $n^*_{i4}$in place of $n_{i4}$ then leads to an unbiased estimate of $\beta_1$.

Farrington et al. present the general case, an associated sandwich estimator for the variance, and also a computationally efficient equivalent approach based on pseudo likelihood.

We note that Roy et al. (2006) present an alternative approach.

### 4. Structured SCCS Models

We are currently exploring several extensions to the basic model.

1. *Hierarchical model: Drugs.* Drugs form drug classes. For example, Vioxx is a Cox-2 inhibitor. Cox-2 inhibitors in turn are non-steroidal anti-inflammatories. A natural extension assumes regression coefficients for drugs from within a single class arise exchangeably from a common prior distribution. This hierarchy could extend to multiple levels.

2. *Hierarchical model: AEs.* AEs also form AE classes. For example, an MI is a cardiovascular thrombotic (CVT) event, a class that includes, for example, ischemic stroke and unstable angina. In turn, CVT events belong to a broader class of cardiovascular events. This extension assumes that the regression coefficients for a particular drug but for different AEs within a class arise from a common prior distribution. Again this hierarchy could extend to multiple levels.

## E. DISCUSSION

We have described self-controlled case series methods for post-approval drug safety risk estimation, some Bayesian and some not. Key advantages of the self-controlled case series approach include:

- SCCS adjusts for all time-invariant multiplicative confounders,

- Estimation requires only cases, and
- A regularized/Bayesian implementation of SCCS scales to large databases with the potential to adjust for large numbers of time-varying covariates.

The main problems with the SCCS approach concern the underlying independence assumptions, in particular, the assumption that events are conditionally independent, and the assumption that the exposure distribution and the observation period must be independent of event times. We described approaches to circumvent these assumptions and these may be useful in some applications.

Furthermore, since SCCS estimates the exposure-outcome association in cases, it ignores data on individuals in the study population that did not experience the outcome event. For example, there may be seasonality driving both the exposure and the outcome, where season is an important time-varying covariate.

To adjust for seasonality, it is helpful to address both (a) the relation between season and the exposure, and (b) the relation between season and the outcome. While SCCS can incorporate time varying covariates, ignoring LOD's rich data on the non-cases limits our power to address (a). In another paper in this issue, we discuss how analyses of data from non-cases can supplement case-based analyses. We note that one possible approach to dealing with the exposure independence issue is to truncate observation time after the first event occurrence. This violates other SCCS assumptions but may still be useful in practice. *Figure 2* shows estimates for a number of drug-outcome pairs with and without truncation. Clearly the truncation does alter some estimated relative risks substantially and future work will evaluate the empirical performance of this approach.

Real-life LODs are noisy and have the potential to introduce all sorts of artifacts and biases into analyses. For example, conditions and the drugs prescribed to treat the conditions are often recorded simultaneously at a single visit to the doctor, even though the condition actually predated the visit. This can introduce "confounding by indication" - the drug used to treat a condition can appear to be caused by the condition. Many such challenges exist and it remains to be seen whether or not false positives will render risk identification in LODs impractical. Since all methods rely on dubious assumptions, future research will focus on establishing the operating characteristics of competing approaches. The Observational Medical Outcomes Partnership (OMOP) has empirically compared the predictive performance of SCCS, multivariate SCCS, and a wide variety of competing methods. Initial results suggest that SCCS is competitive with other methods and multivariate SCCS is a top performer. Nonetheless, the performance of all methods in OMOP leaves much room for improvement.

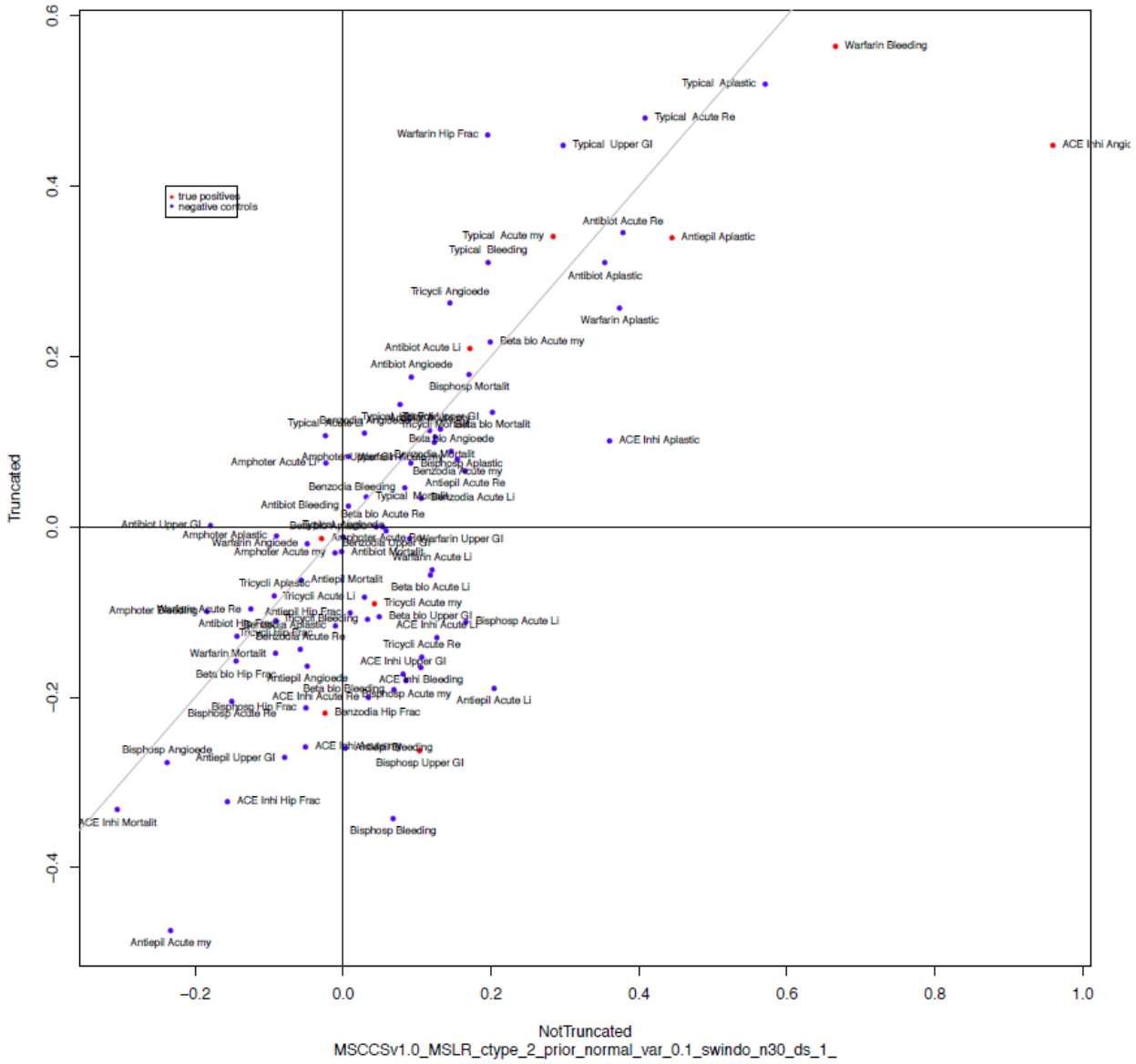


**Figure 2.** Relative risk estimates from SCCS versus truncated SCCS for 53 drug-outcome pairs in the OMOP experiment.

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# IV. APPENDIX: PICTORIAL MODELS CAN HELP ELUCIDATE STATISTICAL MODELS

This Appendix presents several pictures that Mini-Sentinel's Methods Core Workgroup on Case-Based Approaches found helpful supplements when discussing several topics, including: 1) the relationship between Self-Controlled Case Series and Case-Crossover Designs, 2) exposure-trend bias when unidirectional case-crossover designs are nested in an inception cohort design, and 3) exposure misclassification bias due to uncertainty about induction times and about drug intake times in relation to dispensing times and quantities. While the Work Group had little time to discuss the pictures in sufficient depth to reach consensus on their utility, they were found to be interesting enough to include as suggestions in our report. The comments are also suggestions rather than Group conclusions.

An advantage of case-based designs is they involve a relatively small numbers of patients compared with the numbers of subjects in cohort designs. This enables pictures of raw data to be feasible to construct and inspect. Sometimes the pictures can be created in an Excel spreadsheet, allowing for simultaneous visualization of raw data, assumptions and results of simple analyses.

## A. COMPARISON OF STUDY DESIGNS

*Figures 1* and *2* illustrate the relationships among the designs using timelines. The sequence of events in each subject's timeline can be easily converted into a story, helping us to understand reverse-causality bias.

## B. UNIDIRECTIONAL MATCHED-PAIR CASE-CROSSOVER DESIGN IN RELATION TO AN INCEPTION COHORT

*Figure 3* in this appendix illustrates the potential for exposure-trend bias in unidirectional case-crossover designs when an inception cohort is selected, or when a new drug enters the market. The figure shows that short-duration use does not pose much of a problem. Another version of this figure could be made showing much longer exposure duration. In that case, the predominant type of discordant case initially would be exposed in the case-window and unexposed in the control-window. This spreadsheet is, of course, just hypothetical to facilitate explanation. In actuality, Mini-Sentinel might wish to display real drug use data in this fashion so that the potential for exposure-trends bias could be evaluated pictorially, possibly with simulations in the same spreadsheet as the picture.

## C. 'STARS AND STRIPES' DIAGRAMS OF THE EXPOSURES OF DISCORDANT CASES

In our review paper, *Table 1* ranks case-based studies partly by accuracy of exposure measurement. Vaccine safety investigations rank at the top because vaccination is a point exposure administered by a health professional. Investigations of pharmaceuticals taken chronically rank further down in the table. The timing of actual intake of the drug must be inferred from dispensing dates and quantities, and 'days supply' if available. Investigators can find it difficult to discuss analytic strategies in case-based designs when several ingredients of the operational definition of exposure must be juggled, at the same time as wondering about the prevalence of different patterns of exposure.

For example, in an investigation on stimulants as potential triggers of cardiovascular events being conducted by a member of the Work Group, conversations among investigators about drug exposure

patterns were frustrating because there were too many assumptions to juggle. This led to the suggestion that the field needs a standardized type of diagram for visualizing medication use data in a population. It would show at a glance that vaccines are point exposures and antibiotics are near-point exposures. It would show at a glance that antihypertensive use is dominated by continuous users. This led to the idea of 'Stars and Stripes' which was developed into *Figure 4*, a sketch that was presented to the Work Group for brief discussion.

It is hypothesized that a 'Stars and Stripes' diagram will be particularly useful for planning case-crossover analyses, enabling prediction of what might be seen in the case-window just before the onset of illness, and in the control-window.

The idea in *Figure 4* is to sketch an overview of exposure patterns in the general population or the overall database prior to design, so as to assist us in designing the investigation well. After the investigation has been designed, another version of a 'Stars and Stripes' diagram might be helpful. For example, *Figure 5* shows a potential diagram for an inception cohort and a unidirectional case-crossover design. The latter attempts to incorporate the hypothesized Effect Period (minimum and maximum induction time). It would be desirable for the diagram to enable investigators to visualize changes in their assumptions about induction times and the impacts on effect estimates. Such diagrams could be used to display data available from only databases, or they could be enhanced by supplementary population-based observational investigations of true intake patterns associated with dispensing patterns (e.g., migraine-drug use patterns.)

## D. POTENTIAL FORMAT FOR DISPLAY OF CASE-BASED DATA IN MINI-SENTINEL

*Figure 6* is a sketch of a possible format for displaying data on exposed cases periodically updated from distributed databases. The purpose of this format is to facilitate signal detection when little or no preliminary thinking on exposure-effect periods, or case and control windows, has been done. As the mandate of the Work Group is to discuss methods for signal refinement, this figure was only presented and not discussed in detail.

**Figure 3. COMPARISON OF PERSON-TIME INCLUDED IN MATCHED CASE-CROSSOVER DESIGN AND NEW-USER COHORT OF CONTINUOUS USERS WHO STOP AFTER 3 MONTHS**

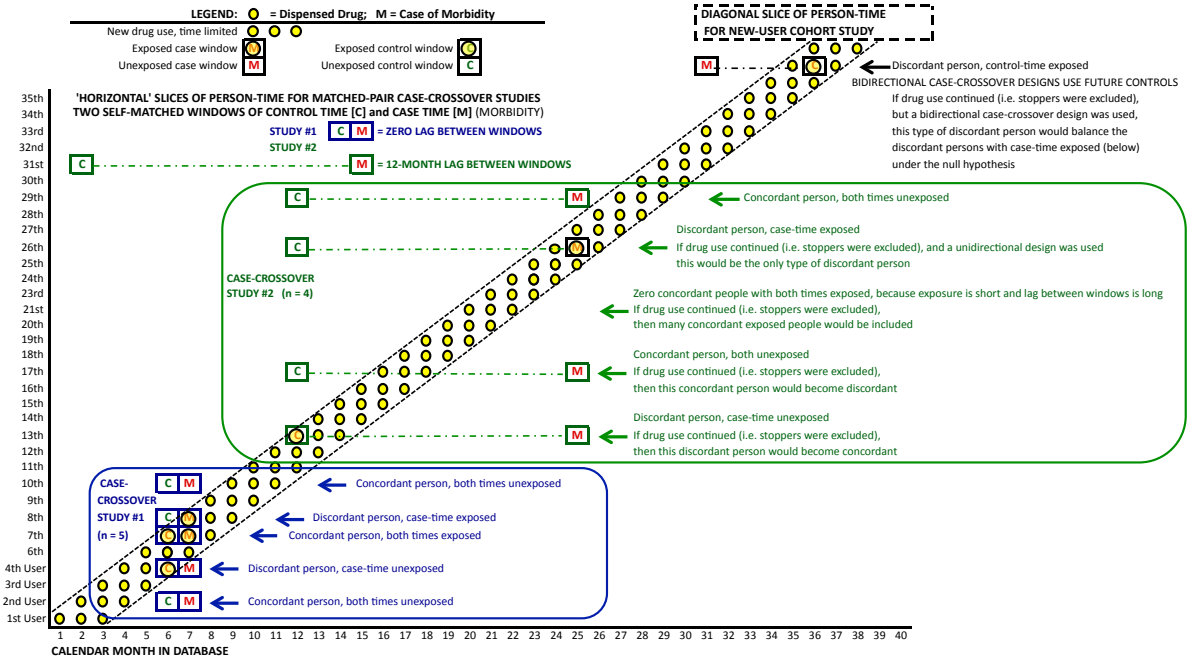

Figure 4. 'Stars and Stripes': Population drug use patterns at-a-glance

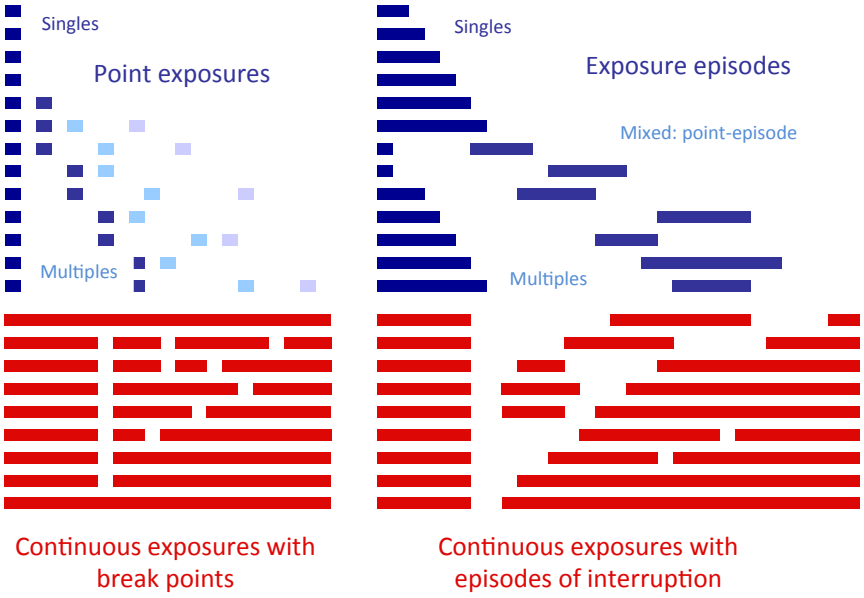

Figure 5. 'Stars and Stripes': Drug use patterns at-a-glance after study design

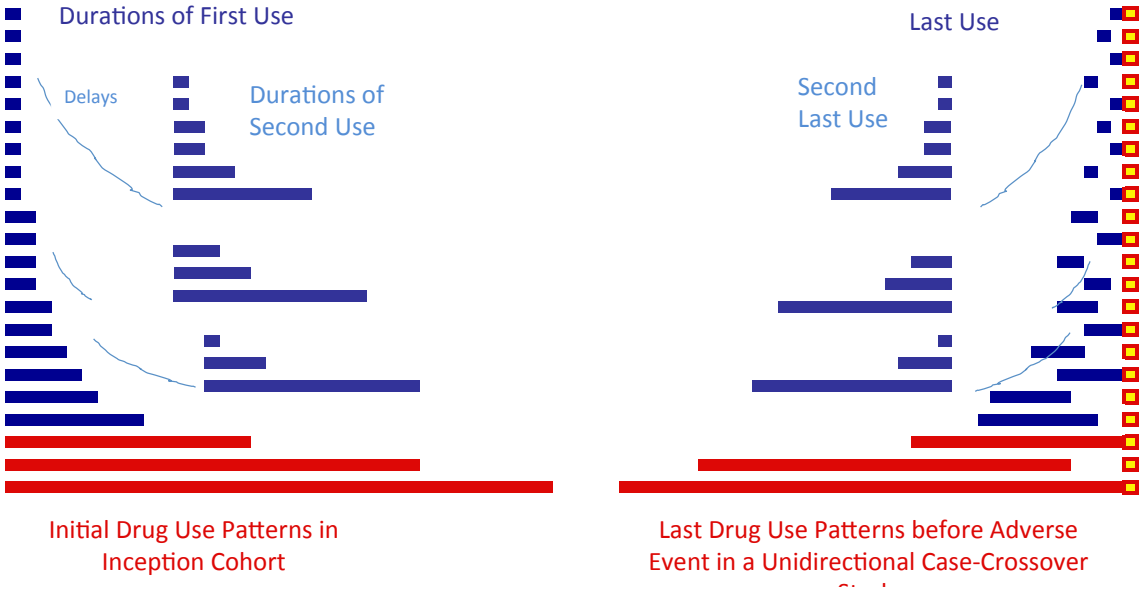

FIGURE 6a. Potential format for display of case-based data for signal generation in Mini-Sentinel

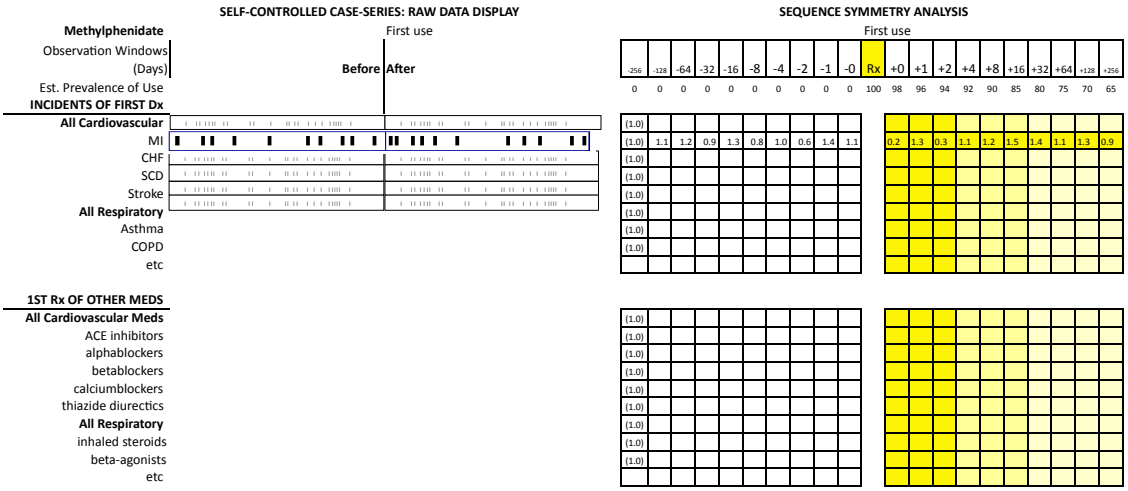

FIGURE 6b. Potential format for display of case-based data for signal generation in Mini-Sentinel