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Title: Grace periods and exposure misclassification in self-controlled case-series studies of drug-drug interactions

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Key words: self-controlled case series, drug-drug interaction, exposure misclassification, grace period, bias

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Title: Grace periods and exposure misclassification in self-controlled case-series studies of drug-drug interactions

Abstract (197/200 words)

The self-controlled case-series (SCCS) research design is increasingly used in pharmacoepidemiologic studies of drug-drug interactions (DDIs), with the target of inference being the incidence rate ratio (IRR) associated with concomitant exposure to the object plus precipitant drug versus the object drug alone. While day-level drug exposure can be inferred from dispensing claims, these inferences may be inaccurate, leading to biased IRRs. Grace periods (periods assuming continued treatment impact after days' supply exhaustion) are frequently used by researchers, but the impact of grace period decisions on bias from exposure misclassification remains unclear. Motivated by an SCCS study examining the potential DDI between clopidogrel (object) and warfarin (precipitant), we investigated bias due to precipitant or object exposure misclassification using simulations. We show that misclassified precipitant treatment always biases the estimated IRR toward the null, whereas misclassified object treatment may lead to bias in either direction or no bias, depending on the scenario. Further, including a grace period for each object dispensing may unintentionally increase the risk of misclassification bias. To minimize such bias, we recommend 1) avoiding the use of grace periods when specifying object drug exposure episodes; and 2) including a washout period following each precipitant exposed period.

Keywords: self-controlled case series, drug-drug interaction, exposure misclassification, grace period, bias

Main text: 3,773/4,000 words

The self-controlled case-series (SCCS) design, initially developed to study vaccine safety,[1] is a case-only study design that uses each person as their own control (**Figure 1**). SCCS analysis involves three steps: 1) identifying individuals who experienced an outcome of interest during specified windows of time termed "observation periods;"[2] 2) classifying observation periods with regard to an exposure of interest into exposed time (termed "focal periods") and unexposed time (termed "referent periods");[2,3] and 3) estimating the incidence rate ratio (IRR) for outcomes that occurs during focal to referent periods.[2] To provide unbiased effect estimates, the SCCS design requires that exposures as well as observation periods should be independent of prior outcome occurrences.[4] Beyond these key assumptions, focal period misspecification can be an important source of bias.[5–8]

The advantages of the SCCS design, such as its inherent control for among-individual confounding and efficiency gained by excluding non-cases, have made it appealing for pharmacoepidemiologic studies of drug-drug interactions (DDIs), where among-person confounding by indication is a major concern.[9] To perform an SCCS to examine a DDI between an object (affected) and a precipitant (affecting) drug, the observation period is defined by person-time exposed to the object for each case. The IRR associated with concomitant treatment is then estimated by comparing the incidence rate during the person-time co-exposed to both precipitant and object drugs (focal) versus that during the person-time exposed to object only (referent).

In SCCS studies of vaccines and other point exposures, the observation, focal, and referent periods usually have a fixed investigator-specified length. In contrast, analytic periods for SCCS studies of chronically administered drugs are often defined with prescription drug dispensing records, using dispensing dates and days' supply information to estimate exposure duration.[10] Further, consecutive prescription records are often concatenated into "continuous" periods of drug exposure using "grace periods" -- time periods for which a person is assumed to remain subject to treatment effects after exhaustion of days' supply to account for factors such as imperfect adherence, and for some drugs, a prolonged duration of effect.[11,12] The impact of this added complexity on bias from analytic period misspecification is poorly understood.

Our study examines the bias from misclassified precipitant or object treatment duration in SCCS DDI studies. A motivating example is first described. We then consider the bias analytically in a simplified scenario, followed by a simulation study to examine realistic scenarios. Finally, we discuss analytic recommendations.

Motivating example

Leonard and colleagues previously used an SCCS to estimate the association between serious bleeding and concomitant treatment with clopidogrel (object) and warfarin (precipitant) versus clopidogrel alone.[13] The study methods are described elsewhere[13] and briefly summarized here. Using 2010–2015 Optum commercial claims data, the study included new clopidogrel users, with the observation period starting on the clopidogrel initiation date. The observation period ended at the earliest of: 1) clopidogrel discontinuation; 2) health plan disenrollment, or 3) the dataset end. The outcome of interest, serious bleeding, was a binary composite outcome including gastrointestinal bleeding and intracranial

hemorrhage. The IRR was estimated by dividing the incidence rate of serious bleeding in the focal period (person-days treated with warfarin and clopidogrel) by that in the referent period (person-days treated with clopidogrel alone), adjusting for time-varying covariates such as non-clopidogrel antiplatelet drug use.

To account for potentially imperfect adherence to clopidogrel, a grace period of seven days was permitted for each 30-day-supply clopidogrel dispensing (i.e., a subject was assumed to remain on clopidogrel for up to seven days after exhaustion of each 30 days' supply, assuming ~80% adherence). When measuring warfarin treatment, no grace period was permitted (i.e., perfect adherence to warfarin was assumed). The estimated IRR was 2.54 (95% confidence interval (CI): 2.38–2.72; **Table 1**), suggesting that the incidence of serious bleeding during concomitant treatment was 2.54 times higher compared to treatment with clopidogrel alone.

However, the IRR estimate varies as assumptions about adherence vary. For example, if the observation period was redefined as clopidogrel-treated person-days without any grace period (i.e., assuming perfect adherence to the object), the estimated IRR was 2.56 (95% CI: 2.39–2.75) -- similar to the original estimate. If a seven-day grace period is included for each 30-day warfarin dispensing (assuming ~80% adherence to the precipitant), the estimated IRR increases to 2.68 (95% CI: 2.50–2.88). There are many additional options for how the grace period might be specified, with a wide range of choices found in the applied literature.[11] To provide guidance on how to specify such grace periods, this article examines the impact of precipitant or object drug misclassification on IRR estimates in an SCCS DDI study.

The SCCS Model

For simplicity, consider a scenario where all cases have one clopidogrel treatment episode of equal length L, with each episode having one warfarin episode of length e_1 ($0 < e_1 < L$), representing the focal period. The remaining person-time within each observation period is unexposed (the referent), with its length denoted by e_0 ($e_0 = L - e_1$). Let R_1 denote the IRR for the focal versus referent periods, and R_0 denote the IRR for the referent period versus itself ($R_0 = 1$). When clopidogrel and/or warfarin are possibly misclassified, let $\tilde{L}$ denote the observation period, $\tilde{e}_1$ denote the focal period length, $\tilde{e}_0$ denote the referent period length, R_1^* denote the IRR of interest under period misspecification, and R_0^* denote the IRR for the misspecified referent period versus itself ($R_0^* = 1$). Assuming no age effect for simplicity, it can be shown the maximum likelihood estimator of R_1^* takes the following form (**Appendix S1**)[5]

$$R_1^* = \frac{\tilde{\pi}_1}{\tilde{e}_1} \Big/ \frac{1-\tilde{\pi}_1}{\tilde{e}_0},$$

where $\tilde{\pi}_k = \frac{R_k^* \tilde{e}_k}{\sum_{s=0}^{1} R_k^* \tilde{e}_s}$. We consider four types of precipitant and/or object misclassification sequentially.

a) $\tilde{e}_1 < e_1$ while $\tilde{L} = L$ (Figure 2A)

This can arise if the measured precipitant treatment episode is shorter than the true precipitant treatment, with the object treatment accurately measured. Let ρ_1 denote the ratio of $\tilde{e}_1$ over e_1, and ρ_0 denote the ratio of $\tilde{e}_0$ over e_0. Previous research has shown that (**Appendix S1**)[5,14]

$$\tilde{\pi}_1 = \frac{R_1\rho_1 e_1}{e_1 R_1 + e_0}.$$

Therefore,

$$R_1^* = R_1 + \frac{1 - R_1}{1 + \frac{e_0}{e_1 R_1(1-\rho_1)}}. \quad (1)$$

Because $0 < \rho_1 < 1$, R_1^* is always biased toward the null. The bias magnitude increases as ρ_1 decreases (precipitant misclassification gets worse). The bias arises because person-time in the focal period is included in the referent period, pushing the incidence rate estimate in the referent period (the denominator) closer to that in the focal period (the numerator).

b) $\tilde{e}_1 > e_1$ while $\tilde{L} = L$ (Figure 2B)

This can arise if the measured precipitant treatment episode is longer than the true precipitant treatment, with the object treatment accurately measured. Again, previous research has shown that R_1^* takes the following form (**Appendix S1**)

$$R_1^* = R_1 - (1 - R_1)\left(\frac{1}{\rho_1} - 1\right). \quad (2)$$

Because $\rho_1 > 1$, R_1^* is always biased toward the null. The bias magnitude increases as ρ_1 increases (precipitant misclassification gets worse). The bias arises because person-time in the referent period is included in the focal period, pushing the incidence rate estimate in the focal period (the numerator) closer to that in the referent period (the denominator).

c) $\tilde{L} < L$ while precipitant treatment is accurately measured (Figure 2C)

This can arise if the measured object treatment episode is shorter than the true object treatment, with the precipitant treatment accurately measured. Even though the precipitant treatment measurement is assumed perfect, $\tilde{e}_1$ may be shorter than e_1 because the focal period identification is conditional on the observation period specification. For this situation, we can show that (**Appendix S1**)

$$\tilde{\pi}_1 = \frac{\rho_1 e_1 R_1}{\rho_1 e_1 R_1 + \rho_0 e_0}.$$

Substituting this into the maximum likelihood estimator of R_1^*, we can show that

$$R_1^* = R_1. \quad (3)$$

Therefore, the IRR estimate is asymptotically unbiased if the measured object treatment is erroneously too short.

d) $\tilde{L} > L$ while precipitant treatment is accurately measured (Figure 2D)

This can arise if the measured object treatment episode is longer than the true object treatment, with the precipitant treatment accurately measured. Additional notation is required because the observation period now includes person-time unexposed to the object, which has not been defined. Let R_2 denote the IRR for precipitant alone versus object alone, and R_3 denote the IRR for no treatment versus object alone. We can show that (**Appendix S1**)

$$\tilde{\pi}_1 = \frac{e_1R_1+(\tilde{e}_1-e_1)R_2}{e_1R_1+e_0+(\tilde{e}_1-e_1)R_2+(\tilde{e}_0-e_0)R_3}.$$

And further,

$$R_1^* = \left(\frac{e_1}{\tilde{e}_1}R_1 + \frac{\tilde{e}_1 - e_1}{\tilde{e}_1}R_2\right) \Bigg/ \left(\frac{e_0}{\tilde{e}_0} + \frac{\tilde{e}_0 - e_0}{\tilde{e}_0}R_3\right). \quad (4)$$

Bias can arise from simultaneous misestimation of the incidence rates during the focal (the numerator) and referent periods (the denominator). Bias direction and magnitude depend on the combined effect of multiple factors, including R_1, R_2, R_3, and the proportion of person-time misclassified for the focal and referent periods.

In addition to the object misclassification extent, the proportion of person-time misclassified may also depend on the precipitant treatment patterns conditional on the true object treatment status. For example, in a scenario where all subjects take the precipitant only when object-treated (**Figure 2D.1**), the proportion of focal period being misclassified is always zero, irrespective of object misclassification extent. In this example, R_1^* moves from R_1 to R_1/R_3 as measured object length increases from the true length to infinity. In another example, if subjects are substantially more likely to take the precipitant when object-untreated, as the measured object length increases, the majority of included cases may become subjects whose precipitant-treated days fall entirely outside the true object episode (**Figure 2D.3**). In this example, R_1^* may move from R_1 to R_2/R_3 as the measured object increases from the true length. In the clopidogrel motivating example, this pattern of misclassification could occur if, based on a given patient's bleeding risk, clinicians advise patients to temporarily discontinue clopidogrel treatment upon warfarin initiation. Therefore, in a realistic scenario where subjects have different precipitant treatment start times and durations, depending on the values of R_1, R_2, and R_3, subjects with different precipitant treatment timings may drive the bias in different directions.

Simulation study

The simulation examines bias from misclassified treatment duration in more realistic scenarios, where precipitant and object episodes are unequal among subjects. We based the simulation setup on the previous study of Leonard and colleagues on the DDI between clopidogrel (object) and warfarin (precipitant).

Simulation setup

Using prior literature estimates,[15–17] a base scenario was simulated where each subject was treated with clopidogrel and warfarin, with each drug doubling the serious bleeding incidence rate when used alone.[15,16] When treated with both, the incidence rate was set to six times the baseline incidence rate without any treatment.[17] In summary, $R_1 = 3$, $R_2 = 1$, and $R_3 = 0.5$.

One object episode and one precipitant episode were simulated per subject. In the base scenario, true object episode length was generated following a Gamma distribution (mean=780 days, standard deviation (SD)=744), mimicking the distribution of clopidogrel-treated days in the motivating example.[13] Similarly, true precipitant episode length was generated to mimic warfarin-treated days specifying a Gamma distribution (mean=180, SD=255). The probability of precipitant initiation on any day was constant, irrespective of the true object treatment status. The incidence rate during object-only

treatment was set at 0.001 per person-day, and those during concomitant treatment, precipitant-only treatment, and no treatment were calculated as R_1, R_2, and R_3 times 0.001 per person-day, respectively. These rates were subsequently used to simulate the event occurrence dates, based on a nonhomogeneous Poisson process ("NHPoisson" package in R,[18] see **Appendix S2–3** for more detailed simulation steps).

We have shown that misclassification bias can be affected by 1) the true IRR of interest (concomitant treatment versus object only); 2) true length of the concomitant treatment relative to object-only treatment; 3) the true IRR associated with precipitant only versus object only; 4) the true IRR associated with no treatment versus object only; and 5) the precipitant treatment prevalence conditional on object treatment status. Therefore, several additional scenarios were simulated exploring the impact of these factors as described in **Table 2**.

We estimated R_1 (the IRR for concomitant treatment versus object alone) assuming misclassification of precipitant, misclassification of object treatment, or both, with the estimate denoted as $\hat{R}_1^*$. We first assumed perfect object measurement with precipitant misclassification, varying the precipitant misclassification extent by varying the ratio of measured to true precipitant treatment lengths from 0.5 to 1.5. We then assumed perfect precipitant measurement, with the ratio of measured to true object treatment lengths varied from 0.5 to 1.5. To explore bias with misclassification of both precipitant and object treatment, using the base scenario described previously, we additionally estimated bias when object measurement was too long, with simultaneous precipitant measurement that was either too long or too short.

Under each treatment misclassification combination, $\hat{R}_1^*$ was obtained across a total of 1,000 simulated datasets of 2,000 subjects, using the *standardsccs* function from the "SCCS" package in R 4.2.0.[19] Means were calculated for $\hat{R}_1^*$ across the 1,000 datasets. Bias on the log scale was calculated as the mean difference between log $\hat{R}_1^*$ and log R_1 in the corresponding scenario. Percentage bias was calculated by dividing the bias on the log scale by log R_1 and multiplying by 100.

Simulation results

In the base scenario as well as all other scenarios, $\hat{R}_1^*$ was always biased toward the null when the measured precipitant treatment was erroneously too short or too long (**Figure 3A**). This is consistent with our expectation based on equations (1) and (2).

When the measured object treatment length was too short, there was no bias across all scenarios (**Figure 3B**), as expected based on equation (3). When the measured object treatment length was too long, bias toward the null was observed across all scenarios (**Figure 3B**), which generally increased as object misclassification extent increased. In contrast, increasing bias towards the null was not observed in the scenario where precipitant initiation was more likely during true object treatment.

In the scenario where the precipitant initiation was more likely during object-treated days, bias remained largely toward the null over range of misclassification assessed. However, as the ratio of measured to true object treatment lengths increased, the percentage bias decreased. We speculate that this occurs because a larger proportion of cases drove the bias away from the null and a smaller proportion drove the bias toward the null. Compared to the base scenario, a larger proportion of the included cases in this scenario had precipitant episodes falling entirely within the true object episodes

(e.g., 66% in this scenario vs. 59% in the base scenario, when the measured object treatment length was 1.5 times the true length). These subjects may drive bias away from the null, because R_1^* moves from $R_1 = 3$ to $\frac{R_1}{R_3} = 6$ as the specified observation period length increases to infinity (equation (4)). It can also be anticipated that, compared to the base scenario, as the specified observation period increases, there is a smaller chance of including new cases whose precipitant episodes fall entirely after the true object treatment. These subjects may drive bias toward the null, because R_1^* could never exceed $\frac{R_2}{R_3} = 2$ among them (equation (4)). In a post-hoc simulation scenario where the probability of precipitant initiation on an object-treated day was set to 15 times that on an object-untreated day, bias away from the null was observed within the object misclassification range assessed (**Table S1**).

In the simulations exploring bias from simultaneous precipitant and object misclassification, increasing precipitant drug misclassification biased increasingly towards the null regardless of object drug misclassification (**Figure S1**). In contrast, the effect of increasing object drug misclassification varied depending on the degree of precipitant drug misclassification. When the ratio of measured to true precipitant length was ~ 0.8 or higher, erroneously long object drug length biased further towards the null (i.e., misclassification from both drugs was additive). In contrast, when the ratio of measured to true precipitant length was < 0.8, erroneously long object drug length let to less bias towards the null. This pattern occurred because the lower-risk person-time associated with neither treatment (R_3) has a greater impact on the specified referent period than on the specified focal period when the measured precipitant length was adequately short.

Example revisited

We have found that when precipitant treatment is misspecified as either too short or too long, the IRR is biased toward the null. Thus, there is risk for bias in applied settings. Omitting a grace period when assessing the precipitant can lead to bias if true adherence to the precipitant is imperfect, since this can lead to "contamination" of the referent period with precipitant-exposed person-days. However, permitting an overly generous grace period for precipitant may also lead to bias, since this can lead to contamination of the focal period with precipitant-unexposed person-days. A straightforward solution to this problem is to consider grace periods to be "washout periods" – i.e., estimating separate IRR for person-time falling within grace periods, thereby minimizing contamination in both the focal and referent periods.

We have also shown that no bias arises from erroneously too short object misclassification alone in the standard SCCS model, since such misclassification does not lead to any person-days misclassified as exposed vs. unexposed. However, bias in either direction is possible, and may be difficult to predict when the object treatment measurement is erroneously too long. Therefore, defining the observation period without a grace period for the object treatment may be less subject to bias. Alternatively, if the observation period is defined permitting a grace period for the object, two additional focal period types can be created to reduce the risk of contamination. Specifically, the following four types of periods could be specified: 1) unexposed to precipitant AND exposed to the non-grace-period object, 2) exposed to precipitant AND the non-grace-period object, 3) exposed to precipitant AND the grace-period object, and 4) unexposed to precipitant AND exposed to the grace-period object.

We apply these approaches to the clopidogrel and warfarin example. The clopidogrel exposed observation periods were first redefined without a grace period. Within these new observation periods, the focal periods were defined without a grace period for warfarin. A washout period of up to seven days was then specified following each 30-day warfarin dispensing (assuming ~80% adherence to warfarin). The estimated IRR for the focal period (concomitant treatment versus clopidogrel alone) was 2.83 (95% CI: 2.63–3.03; **Table 3**), higher than the estimate of 2.68 if including warfarin's grace periods in the focal periods. To examine the robustness of the results to the warfarin adherence assumption, it may be reasonable to conduct a sensitivity analysis with the washout length selected using a data-driven approach (**Tables S2**–**3** and **Figure S2**).

Alternatively, we permitted a seven-day grace period for each 30-day-supply clopidogrel dispensing as the original analysis did when defining the observation period. However, when defining the focal periods, the grace and non-grace periods for clopidogrel were distinguished as described earlier. The IRR for warfarin+non-grace-period clopidogrel versus non-grace-period clopidogrel only was 2.84 (95% CI: 2.65–3.04; **Table 3**). By contrast, the IRR for warfarin during grace-period clopidogrel was substantially lower (1.09, 95% CI: 0.90–1.31).

Discussion

We examined how misclassified precipitant and object treatment durations biases the IRR in DDI studies using the standard SCCS design. We found that when the object is perfectly measured, precipitant treatment misclassification is analogous to the well investigated focal period misspecification in SCCS studies in the context of point exposures and can lead only to bias toward the null.[5] Notably, erroneously short object treatment length does not lead to bias. In contrast, if measured object treatment is erroneously long, there can be bias *toward or away* from the null. This is because the extended observation period will include more than two underlying risk levels (concomitant, object-only, precipitant-only, and neither treatment), and bias in either direction can arise from misclassification in a multi-level exposure variable.[20] The bias direction from erroneously long object misclassification can be unpredictable if accurate effect estimates for object monotherapy, precipitant monotherapy, and concomitant treatment are unavailable.

We propose a simple but effective approach to mitigate bias from mismeasured precipitant and/or object treatment durations. First, when defining the observation period based on the object treatment status, we recommend including only person-days that are highly likely to be object-treated (e.g., not including a grace period for the object, unless there is strong evidence supporting that subjects remain on the object during grace periods). This minimizes the risk of misclassifying object-untreated person-days into either concomitantly treated focal or object-only referent periods. Alternatively, the observation period can be defined permitting a grace period for each object dispensing, as long as the analytic periods are defined distinguishing between the grace and non-grace periods. We similarly recommend including into the focal period only person-days that are highly likely to be precipitant-treated (e.g., not implementing a grace period for the precipitant) and to include a generous washout period following each focal period. This reduces the risk of misclassifying person-days still at risk into the referent period and the risk of misclassifying person-days no longer at risk into the focal period. The washout period may be specified based on existing knowledge, and sensitivity analyses using data-driven washout may be appropriate. In addition to the method presented in **Table S2**, the spline-based

SCCS method may be helpful in exploring the optimal washout period length.[8] Importantly, the recommendation to specify a washout period following each focal period also applies SCCS studies beyond the DDI context.[21]

This study has limitations. First, this study focuses on the standard SCCS model, where the event incidence rate is assumed constant within the same focal/referent period, and outcome-independent exposures and observation periods are assumed. In reality, the DDI effect may vary over the duration of concomitant treatment.[9] In addition, SCCS assumptions may often be violated. Patients may stop taking the precipitant drug, object drug, or both, following an outcome occurrence (with or without clinician supervision). Notably, such treatment discontinuation may not be promptly captured by the dispensing records, leading to outcome-dependent exposure misclassification. Bias from interaction between the mismeasured treatment and SCCS assumption violations deserves future research. Second, this study assumes that the person-days covered by the recorded days' supply are truly treated and at the corresponding risk level. In reality, early treatment discontinuation not reflected in days' supply is possible. The exact time of such discontinuation is usually not observed. Nevertheless, if it is suspected that patients may have discontinued treatment following a certain time point, the spirit of our recommendations still apply, namely to only include person-days highly likely to be precipitant-treated into the focal period; and person-days highly likely to be object-treated into the referent period. Thus, specification of additional analytic periods based on hypothesized patterns of adherence could be considered carefully in a case-by-case fashion. Third, our simulation setup is somewhat simplified, allowing for a single object episode and a single precipitant episode for each subject, whereas subjects may experience multiple dispensings, consecutively or with gaps. Finally, although we examined multiple simulation scenarios, they do not represent all possible scenarios.

In summary, in SCCS DDI studies, precipitant or object treatment misclassification can both bias the estimated association between the concomitant treatment and the outcome, with the bias not necessarily toward the null. We recommend defining the observation period based on conservatively short object treatment measurement as well as including a washout period following each concomitantly treated focal period.

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Table 1. Estimated incidence rate ratios associated with concomitant treatment based on varying adherence assumptions in the motivating example[a]

Observation period	Concomitantly treated focal period	Number of person-days in the observation period	Number of person-days in the focal period (%)	Focal period: number of events (crude incidence)	Referent period: number of events (crude incidence)	Concomitant treatment IRR (95% CI)
Seven-day grace period permitted for clopidogrel	No grace period permitted for warfarin	16,285,312	770,565 (4.7%)	3,163 (4.10×10^{-3} event per day)	29,676 (1.91×10^{-3} event per day)	2.54 (95% CI: 2.38–2.72)
No grace period permitted for clopidogrel	No grace period permitted for warfarin	14,483,049	696,909 (4.8%)	2,955 (4.24×10^{-3} event per day)	27,144 (1.97×10^{-3} event per day)	2.56 (95% CI: 2.39–2.75)
No grace period permitted for clopidogrel	Seven-day grace period permitted for warfarin	14,483,049	754,946 (5.2%)	3,200 (4.24×10^{-3} event per day)	26,899 (1.96×10^{-3} event per day)	2.68 (95% CI: 2.50–2.88)

IRR=incidence rate ratio, CI=confidence interval

[a]The table displays, in the motivating example, the estimated incidence rate ratios associated with concomitant treatment versus object-treatment only, along with observed person-time, number of events, and incidence rates, when using varying definitions of the observation period and the focal period.

Table 2. Simulation parameters for each scenario

Scenario[a]	R_1	R_2	R_3	Mean (SD) object episode length	Mean (SD) precipitant episode length	Probability of precipitant initiation on an object-treated vs -untreated day
Base	3	1	0.5	780 (744)	180 (255)	1
(1) Higher R_1 The IRR associated with concomitant treatment versus object alone was set to a higher value.	3.5[b]	1	0.5	780 (744)	180 (255)	1
(2) Lower R_1 The IRR associated with concomitant treatment versus object alone was set to a lower value.	2.5[b]	1	0.5	780 (744)	180 (255)	1
(3) Lower R_2, R_3 Both the IRR associated with precipitant alone versus object alone and the IRR associated with no treatment versus object alone were set to lower values, while keeping the ratio of R_2 to R_3 constant. This corresponds to a situation where both object and precipitant monotherapies have an effect on the outcome, but the object-only effect was greater than the precipitant-only effect.	3	0.2[b]	0.1[b]	780 (744)	180 (255)	1
(4) Lower R_2 The IRR associated with precipitant alone versus object alone was set to a lower value. This corresponds to a situation where the precipitant by itself has no effect on the event incidence, as might occur in a pharmacokinetic rather than pharmacodynamic interaction.	3	0.5[b]	0.5	780 (744)	180 (255)	1
(5) Longer precipitant The mean precipitant treatment length was set to a longer value.	3	1	0.5	780 (744)	540 (764)[b]	1
(6) Shorter precipitant The mean precipitant treatment length was set to a shorter value.	3	1	0.5	780 (744)	90 (127)[b]	1
(7) More frequent precipitant initiation when object-treated The probability of precipitant initiation on an object-treated day was set to three times that on day without the object.	3	1	0.5	780 (744)	180 (255)	3[b]
(8) Less frequent precipitant initiation when object-treated The probability of precipitant initiation on an object-untreated day was set to three times that on an object-treated day.	3	1	0.5	780 (744)	180 (255)	1/3[b]

IRR=incidence rate ratio, SD=standard deviation, R_1=incidence rate ratio associated with concomitant treatment versus object alone, R_2=incidence rate ratio associated with precipitant alone versus object alone, R_3=incidence rate ratio associated with no treatment versus object alone

[a]The table displays the parameters specified in each simulation scenario for data generation.

[b]Parameters that are set to differ from the base scenario.

Table 3. Estimated incidence rate ratios associated with concomitant treatment using proposed methods in the motivating example[a]

Method	Object	Precipitant	Analytic period	IRR	95% CI
1	No grace period permitted for clopidogrel	Up to seven-day washout included following each warfarin dispensing	Precipitant + object (of primary interest)	2.83	2.63–3.03
			Washout + object	2.16	1.88–2.48
			Reference: No precipitant + object	1	-
2	Seven-day grace period permitted for clopidogrel	Up to seven-day washout included following each warfarin dispensing	Precipitant + non-grace-period object (of primary interest)	2.84	2.65–3.04
			Washout + non-grace-period object	2.16	1.88–2.48
			Precipitant + grace-period object	1.09	0.90–1.31
			Washout + grace-period object	1.23	0.91–1.67
			No precipitant + grace-period object	0.42	0.40–0.45
			Reference: No precipitant + non-grace-period object	1	-

IRR=incidence rate ratio, CI=confidence interval

[a]The table displays, in the motivating example, estimated incidence rate ratios associated with concomitant treatment versus object-treatment only when using the proposed method to specify analytic periods.

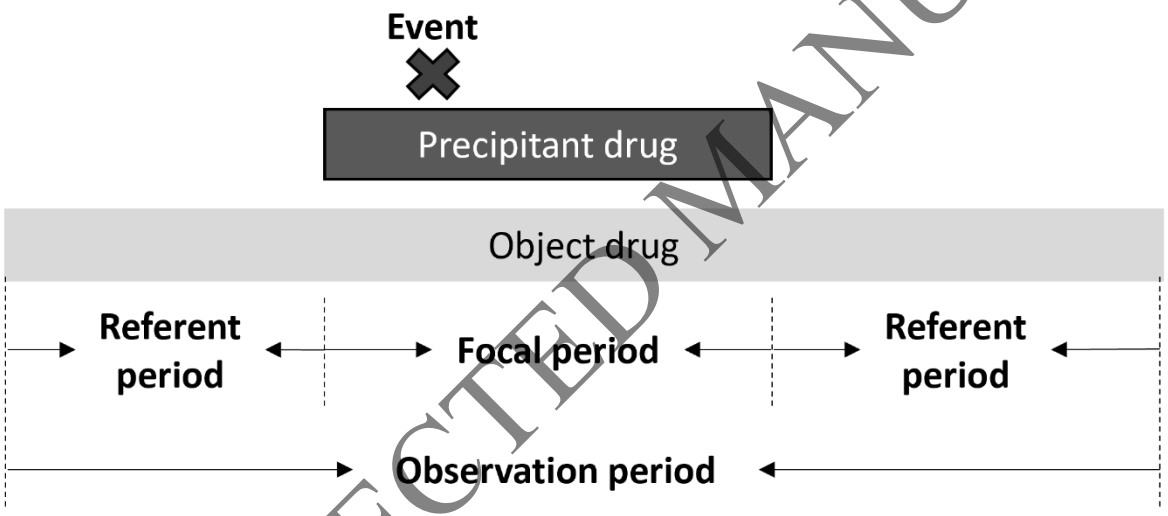

Figure 1. Focal and referent period specification in a self-controlled case series study of drug-drug interactions

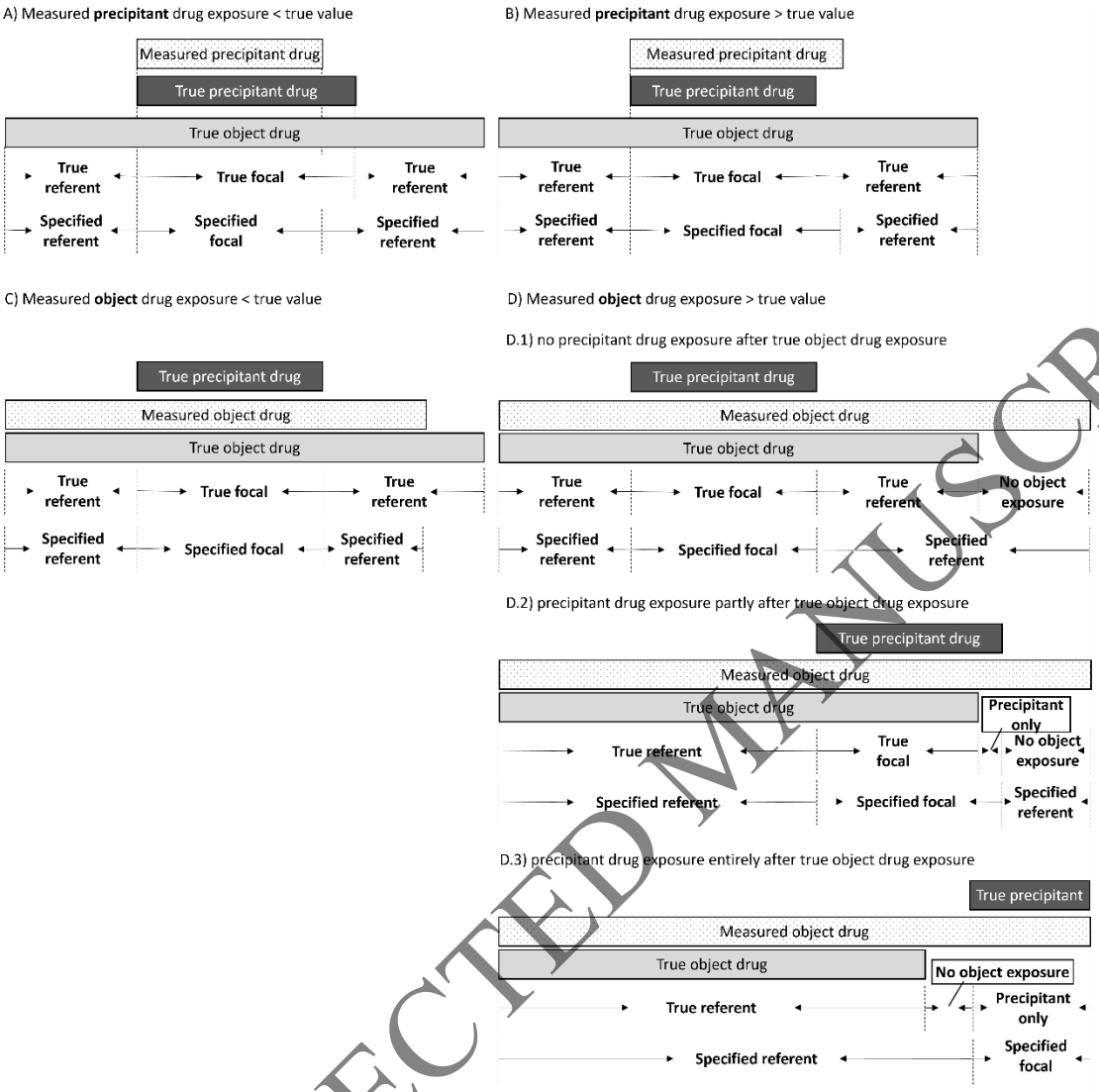

Figure 2. Focal and referent period specification in a self-controlled case series study of drug-drug interactions with misclassified precipitant or object treatment duration

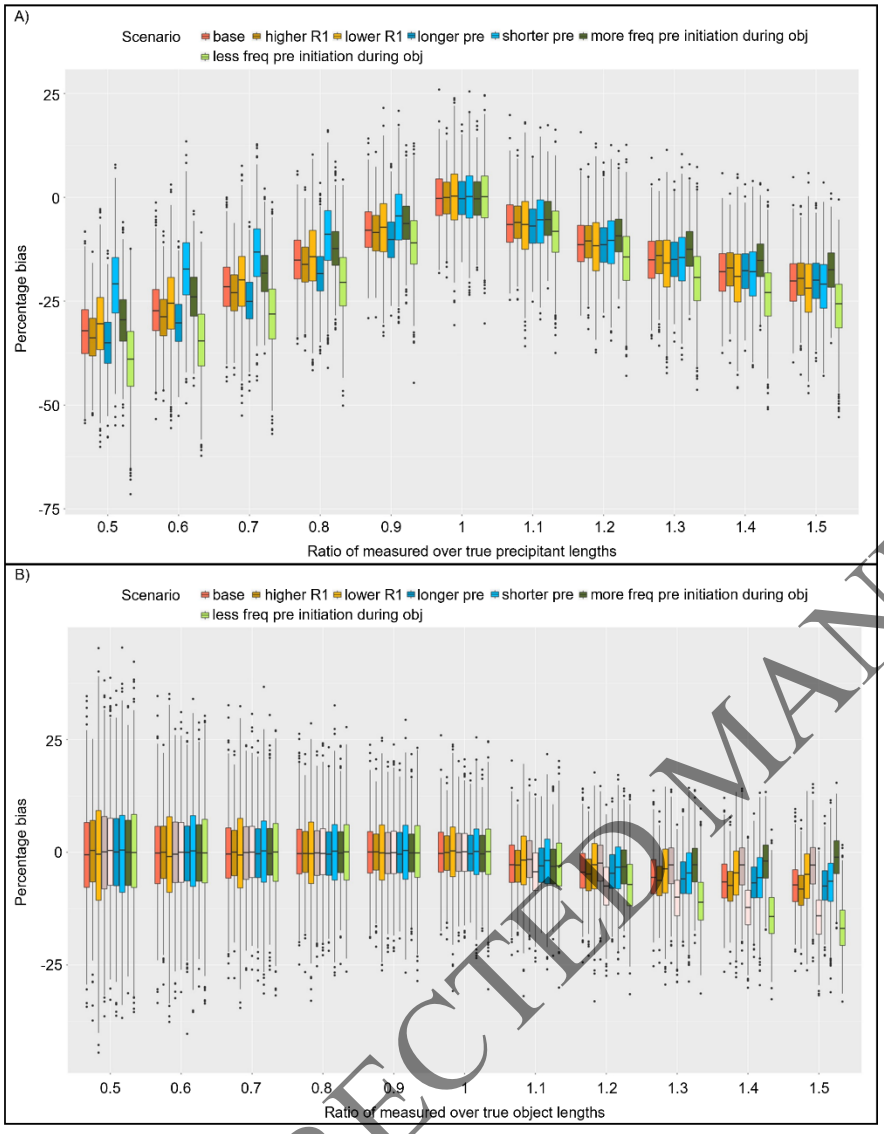

Figure 3. Box plot of percentage bias in the estimated incidence rate ratio associated with concomitant treatment on the log scale from misclassified treatment across different scenarios. For each box plot, the box depicts the interquartile range (IQR) of the estimates across simulation iterations, the horizontal line in the middle of the box depicts the median, the lower whisker depicts the lowest estimate within 1.5 times the IQR from the 25th quartile, and the upper whisker depicts the highest estimate within 1.5 times the IQR from the 75th quartile.• **Panel A)** Percentage bias from misclassified precipitant treatment • **Panel B)** Percentage bias from misclassified object treatment

[a]The results under misclassified precipitant exposure in the scenarios of "lower R2, R3" and "lower R2" were omitted since they were unlikely to impact the results when the object exposure was correctly measured.

[b]The average numbers of cases included out of 2,000 subjects in each simulated dataset are available in **Table S4**