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Early Steps in the Development of a Claims-Based Targeted Healthcare Safety Monitoring System and Application to Three Empirical Examples

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Abstract

Background: Several efforts are under way to develop and test methods for prospective drug safety monitoring using large, electronic claims databases. Prospective monitoring systems must incorporate signalling algorithms and techniques to mitigate confounding in order to minimize false positive and false negative signals due to chance and bias.

Objective: The aim of the study was to describe a prototypical targeted active safety monitoring system and apply the framework to three empirical examples.

Methods: We performed sequential, targeted safety monitoring in three known drug/adverse event (AE) pairs: (i) paroxetine/upper gastrointestinal (UGI) bleed; (ii) lisinopril/angioedema; (iii) ciprofloxacin/Achilles tendon rupture (ATR). Data on new users of the drugs of interest were extracted from the HealthCore Integrated Research Database. New users were matched by propensity score to new users of comparator drugs in each example. Analyses were conducted sequentially to emulate prospective monitoring. Two signalling rules – a maximum sequential probability ratio test and an effect estimate-based approach – were applied to sequential, matched cohorts to identify signals within the system.

Results: Signals were identified for all three examples: paroxetine/UGI bleed in the seventh monitoring cycle, within 2 calendar years of sequential data; lisinopril/angioedema in the second cycle, within the first monitoring year; ciprofloxacin/ATR in the tenth cycle, within the fifth year.

Conclusion: In this proof of concept, our targeted, active monitoring system provides an alternative to systems currently in the literature. Our system

employs a sequential, propensity score-matched framework and signalling rules for prospective drug safety monitoring and identified signals for all three adverse drug reactions evaluated.

Background

The US FDA Amendment Act of 2007 (FDAAA) mandated the FDA to establish a prospective drug safety surveillance system using electronic healthcare data.[1] Similar efforts, such as the EU-ADR project, are underway in European countries.[2] Electronic databases that will feed these systems generally capture healthcare data for large, geographically diverse populations that cover care administered across various healthcare settings, from physician office visits to acute and long-term inpatient stays. Utilization of biologics, drugs, medical devices and procedures are generally captured in such settings, as well as some laboratory tests and results, offering a rich source of information for therapeutic exposures, and enabling comparative effectiveness and safety evaluations.[3] Unlike passive mechanisms relying on spontaneous adverse event (SAE) reporting, these databases offer the benefit of providing systematic outcome ascertainment and denominator data, and are not subject to the Weber effect in reporting of SAEs. In addition, electronic healthcare data allow for the monitoring of common adverse events (AEs), such as acute myocardial infarction, for which causal relations with drugs are difficult to infer among individual patients in clinical practice. These databases are often used for retrospective drug safety evaluation based on methods that pay particular attention to issues of potential confounding, misclassification and selection bias.[4] In the prospective context, active monitoring of pre-specified drug and AE pairs can closely resemble ordinary pharmacoepidemiology studies. However, issues of bias become even more salient in this context, as they can more directly influence regulatory decision making or commercial manufacturers' risk mitigation strategies.

To be effective, any system to actively monitor pre-specified drug and AE pairs needs to incorporate design features to minimize both false positive and false negative signalling. Methods that lead to early notification of potential signals are useful only to the extent that they accurately detect true unbiased associations of concern. A system that unnecessarily raises alarms at the targeted signal detection stage (following initial, untargeted signal generation) based on false positive detection does not help patients, caregivers or regulatory authorities and may misdirect resources, hindering stakeholders' ability to implement informed decision making. Similarly, when a drug/AE association truly exists, a system that fails to generate a signal in a timely manner represents a lost opportunity to reduce morbidity or mortality.

Several efforts are under way to develop and test monitoring systems and methods within claims data environments.[5-11] The essence of these systems and methods is accurate and timely signal detection.

In the context of three empirical examples, we describe the analytical framework of a targeted, active prospective safety monitoring system that leverages the breadth of information available in a large longitudinal claims data source, and that combines established methods for signalling and extensive confounding adjustment.

Methods

Overview

Using administrative claims data, we emulated open cohort monitoring scenarios for three known drug safety issues: (i) paroxetine and severe upper gastrointestinal (UGI) bleed; (ii) lisinopril and angioedema; and (iii) ciprofloxacin and Achilles tendon rupture (ATR). These monitoring scenarios were selected because of the indications of known adverse drug reactions in the literature, the variation in risk window periods, as well as

for their feasibility of investigation within the claims data environment.

Cohort Identification and Exposure and Outcome Definitions

The study cohorts for the pilot-test examples were drawn from the HealthCore Integrated Research Database (HIRD), which comprises a population of over 32 million commercially insured members of 14 health plans in the US (Southeast, Mid-Atlantic, Northeast, Central and Western regions). Comparator cohorts were selected as users of drugs with similar indications to the drugs under study, but without suspected association with the outcomes of interest.

Monitoring Scenario 1: Selective Serotonin Reuptake Inhibitors and Severe Upper Gastrointestinal Bleed

The first monitoring scenario examined the risk of severe UGI bleed among new users of the antidepressant paroxetine. New use was defined by no evidence of antidepressant use in the 6 months prior to paroxetine initiation.[12-22] The comparator cohort comprised new users of tricyclic antidepressants (TCAs) with low affinity for serotonin receptors (i.e. desipramine, nortriptyline and doxepin). Both cohorts were identified between 1 January 2004 and 31 December 2007 (drug codes used to identify patients in pharmacy claims are available from the authors), when adequate uptake of paroxetine would have been evident in the available claims data.

We defined the exposure risk window as the period covering the 90 days following paroxetine or TCA initiation (index date). Each incident user was followed from the index date to the earliest of index date plus 90 days, the end of eligibility, a severe UGI bleed event or the end of the monitoring timeframe. We defined severe UGI bleed using a claims-based algorithm validated by Wahl et al.[23] and derived using codes reported by Raiford et al.[24] and Andrade et al.[25] Patients entering the study were allowed to re-enter the analysis in the other treatment group (e.g. if they first entered as paroxetine initiators they were permitted to re-enter only as TCA users), after completing a 6-month antidepressant-free (washout) period. The maximum number of exposure segments a person could have in the study was two (i.e. one for paroxetine and one for TCA).

Monitoring Scenario 2: Lisinopril and Angioedema

The second monitoring scenario evaluated the risk of angioedema among new users of lisinopril, an angiotensin-converting enzyme (ACE) inhibitor. New use was defined by no ACE inhibitor or angiotensin receptor blocker (ARB) use in the 6 months prior to initiation. New users of lisinopril were compared with a cohort of new users of ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) between 1 January 2001 and 31 October 2008. This time period included 3 years (2001–3) when data from only two health plans were available.

Each incident user of lisinopril or the comparator ARBs was followed for the entire first continuous therapy segment (defined, in days, as consecutive fills bridged by gaps between fills of up to the days' supply plus 30 days) for identification of angioedema.[26-29] Patients contributed person-time from the index date until the first treatment discontinuation, switching to the comparator drug (or drug class), end of eligibility, incidence of angioedema or the end of the monitoring timeframe, whichever came first. Patients entering the study were not allowed to re-enter the study on a comparator drug. We defined angioedema as the first occurrence of a claim with International Classification of Diseases Ninth Edition (ICD-9) diagnosis code 995.1 as defined by Brown et al.[8]

Monitoring Scenario 3: Ciprofloxacin and Achilles Tendon Rupture or Repair

The third monitoring scenario compared the risk of ATR in patients with a new exposure (as defined by no fluoroquinolone or macrolide use in the 6 months prior to initiation) to ciprofloxacin[30-36] with those with a new macrolide exposure between 1 July 2001 and 30 April 2008. As in the second monitoring scenario, this time period included 3 years (2001–3) when data from only two health plans were available.

The exposure risk window was defined as the period covering 183 days following incident use

of ciprofloxacin or of a comparator macrolide. Each incident user was followed from the index date to the first of index date plus 183 days, end of eligibility, incidence of a tendon rupture or the end of the monitoring timeframe. Patients were not allowed to re-enter the analysis. We originally defined ATR as first occurrence of a claim with ICD-9 codes 727.6 (any tendon rupture), 727.71 (Achilles tendonopathy), 727.0 (synovitus) or 726 (enthesopathy), or Current Procedural Terminology® (CPT®) codes 27650, 27652 or 27654 (Achilles tendon repair), as found in the general literature.[30-36] However, 'any tendon rupture', tendonopathy, synovitis and enthesopathy proved to be non-specific for the endpoint and did not result in a valid signal. The outcome was then refined to include only the more serious event of an ATR (ICD-9 code 727.67) or Achilles tendon repair (CPT® codes 27650, 27652 or 27654), as examined and confirmed through chart review by Seeger et al.[30]

All study materials were handled in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Monitoring Cycles and Propensity Score Matching

To emulate a prospective analysis, the data were divided into fixed calendar periods (i.e. monitoring cycles) of 3 months for the paroxetine example and 6 months for the lisinopril and ciprofloxacin examples. This allowed for sequential analyses of data as if they were accumulating prospectively. Patients with index dates in the first monitoring cycle were propensity score (PS) matched prior to performing analyses, with follow-up for patients whose risk window extended beyond the calendar period truncated as of the end of that first calendar period (initially, until data from the second cycle were added). For example, in figure 1, patients A and B initiated therapy in the first monitoring cycle. Together with all other patients with index dates in this cycle, they form the cycle 1 cohort. A 2×2 table was populated based on the cycle 1 cohort and crude analyses performed after PS matching. When cycle 2 data became available, follow-up data for patients with index dates in cycle 1 were added to the truncated cycle 1 data. A separate PS model was fit for hypothetical patients C and D and all other patients with index dates in cycle 2 and these patients were matched, from which another 2×2 table was populated. The cycle-specific 2×2 tables were aggregated over time to form a cumulative cohort on which subsequent analyses were based.

In each monitoring cycle, PS models included a set of empirical covariates and pre-defined covariates for each scenario, all measured in the 183 days preceding the patients' index dates. The empirical covariates were derived from the

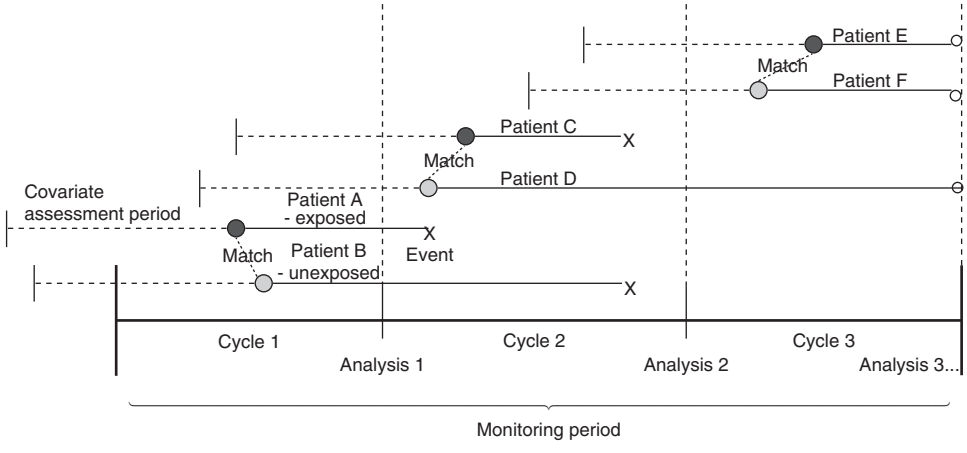


Fig. 1. Monitoring cycles.

100 most frequently occurring ICD-9 codes, CPT codes and drug claims coded by Generic Product Identifier (GPI) in the pre-index baseline period. PS estimation and matching was performed separately in each monitoring cycle to ensure that patients in the drug group of interest were time-matched to their respective comparator groups and to address confounding due to changing prescribing patterns over time. PS matching was performed using the greedy matching algorithm described by Parsons.[37]

Analysis and Signalling Rules

At the end of each monitoring cycle and after the formation of PS-matched cohorts, measures of association for each of the drug cohort/AE pairs were calculated. In the case of paroxetine (scenario 1) and ciprofloxacin (scenario 3) – scenarios with fixed exposure windows – risk ratios (RR) and risk differences were calculated. In the case of lisinopril (scenario 2), for which the exposure window and thus person-time varied with duration of therapy, rate ratios and rate differences were calculated. We also computed values for the maximum sequential probability ratio test (maxSPRT). maxSPRT is a sequential testing approach that has been used for vaccine and drug safety monitoring[8,38,39] and utilizes either a background event frequency (where such is known) or the comparator experience (in which a matched sample provides comparator event frequencies, as in our three scenarios) in order to establish a benchmark against which to calculate the maxSPRT test statistic. The null hypothesis of the maxSPRT utilized with a comparator group is, essentially, unity, or no difference in rates (Poisson approach) or numbers of events (binomial approach) between the groups.

Pre-defined thresholds and maximum monitoring times were used as inputs for two signal detection rules: (i) the first cycle in which the maxSPRT exceeded a pre-specified critical value (set so as to reject the null hypothesis of a relative risk or rate of 1 when the test statistic exceeds this value) based on an *a priori* overall exceedence probability ($\alpha < 0.05$); and (ii) a strength-of-association approach triggered by the point estimate (RR) surpassing a pre-specified value (RR ≥2.0 or Log of Relative Risk/Rate (lnRR) ≥0.69) during three consecutive monitoring cycles. The former is currently used in vaccine safety monitoring[7,38,40] and the latter is an analogue to an approach to disproportionality analyses in data mining of SAEs that uses, for example, a proportional reporting ratio of ≥2.0.[41] Zero cell count corrections were made during monitoring cycles in which no events were observed, in order to compute effect estimates for algorithm 2.[42] This correction leads to effect estimates that can exceed the threshold for algorithm 2 when one event in the exposed group and no events in the unexposed group are observed. This is undesirable because of the instability of the estimate in cycles with few events. We therefore imposed the requirement of a minimum of five events to be observed before the strength-of-association algorithm can be initiated. This requirement is consistent with that of the binomial application of maxSPRT in which exposed and unexposed are matched in a 1 : 1 ratio.[43]

Results

Exposure and Event Frequencies

In the first monitoring scenario, a total of 28 602 patients initiating paroxetine were PS-matched 1 : 1 to patients initiating a TCA over the fourteen 3-month monitoring cycles covering the period 1 July 2004–31 December 2007. A total of 24 (0.08%) and 14 (0.05%) severe UGI bleed events were identified among matched paroxetine and TCA users, respectively. In the second scenario, 153 605 new users of lisinopril were matched to the same number of ARB initiators over the fourteen 6-month cycles occurring between 1 July 2001 and 30 June 2008. We identified 231 cases of angioedema over a total of 85 610 person-years (PY) of follow-up among lisinopril users (2.70 incident events per 1000 PY) and 113 cases over 80 374 PY of follow-up among ARB users (1.41 incident events per 1000 PY). A total of 530 235 patients initiating ciprofloxacin were matched 1 : 1 to patients initiating a macrolide antibiotic over the fourteen 6-month cycles occurring between

1 July 2001 and 30 June 2008. A total of 13 (0.0025%) and 9 (0.0017%) of those patients exposed to ciprofloxacin and macrolides, respectively, were identified as having had an ATR.

Signal Strengthening Analysis

The overall cumulative lnRR observed in scenario 1 for the entire monitoring timeframe was 0.539 (figure 2a). The maxSPRT log likelihood ratio never exceeded its critical value threshold. However, an elevated risk (i.e. lnRR >0.69) was observed in periods 5, 6 and 7, triggering the effect estimate-based rule.

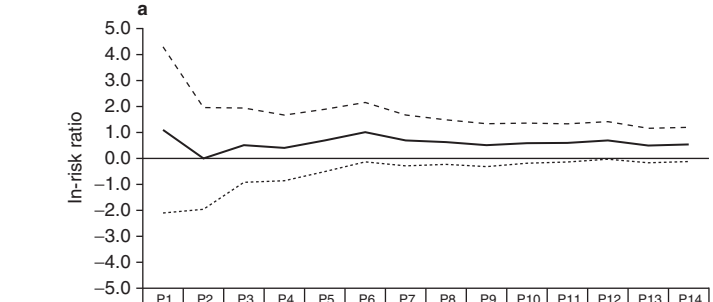
In the second monitoring scenario, a large increase in the relative rate of angioedema associated with lisinopril was observed immediately (figure 2b). By the end of the monitoring timeframe, the lnRR had decreased from 1.501 in the second cycle to 0.652. The maxSPRT exceeded the critical value in the second monitoring cycle and an lnRR of >0.69 was observed in each of the first three monitoring cycles, as well as thereafter.

In scenario 3, neither algorithm signalled using the broader definition in which codes non-specific for the endpoint were included. Utilizing the definition consistent with Seeger et al.[30] resulted in a greatly reduced number of observed events, with only one event in new ciprofloxacin users and no events in the new macrolide users by the end of seven monitoring cycles. The strength-of-association approach did not begin contributing to the signalling algorithm until cycle 9, when at least five events (n = 10) were observed in the ciprofloxacin group (figure 2c). Algorithm 2 then triggered during cycle 11, while the maxSPRT surpassed the critical value during the tenth cycle. By the end of the monitoring timeframe, we no longer observed an elevated risk based on the cumulative number of events in both groups.

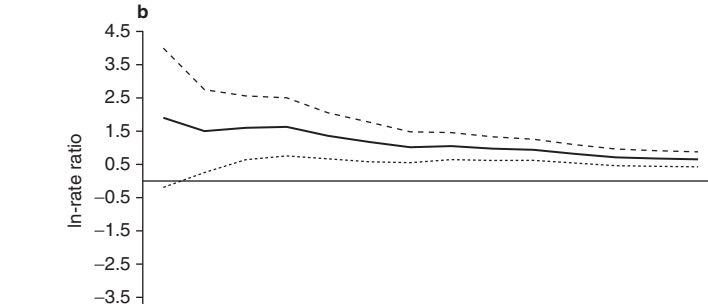
Discussion

In this early stage of the development of the system, we have modelled monitoring strategies for three potential drug safety scenarios. In the first monitoring scenario, a potential signal with severe UGI bleed in paroxetine users was identified, when effect estimates for three consecutive monitoring cycles (periods 5–7) exceeded the predefined threshold. A signal for an increased rate of angioedema was identified early in the monitoring process by both algorithms in the second example with lisinopril. Monitoring scenario three investigated the risk of ATR in ciprofloxacin users. A signal was identified via the maxSPRT in time period 10, and via the effect estimate-based rule in time period 12.

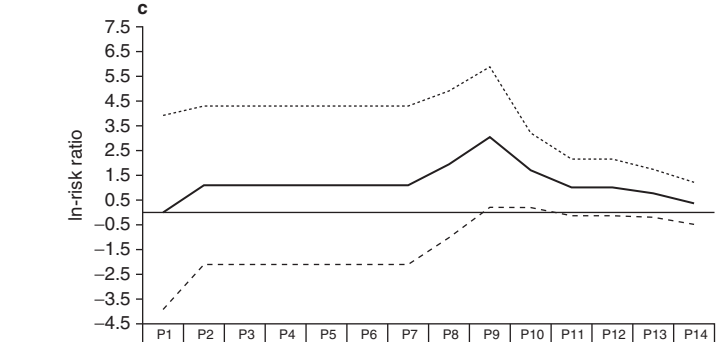
Several signal identification algorithms for prospective drug safety monitoring and for post-procedure safety monitoring have been proposed.[44-49] These activities are distinct from targeted safety monitoring in which particular drug/AE pairs are examined and monitored as pre-specified targets. In three monitoring scenarios, we employed the maxSPRT along with a simple, pragmatic approach based on effect size to perform targeted safety monitoring. It is not yet known how the performance characteristics of various signalling rules compare, but this is an active area of investigation. Further work is currently being conducted using empirical and simulated data to compare various algorithms in terms of timing, sensitivity and false positive rates. It is important to note that aspects of the methods reported here are not novel in and of themselves as separate components, but taken together offer a proof of concept that builds on existing literature. For example, construction of the sequential PS-matched cohort approach, but without sequential testing, has been previously described,[50,51] as has the application of maxSPRT to drug safety.[8,39] However, to the best of our knowledge, this is the first report to describe the combination of the two, with the intention of addressing confounding to minimize the potential for false positives and false negatives due to bias, coupled with the use of signalling algorithms to minimize false positives due to chance. Reducing effect estimate or signalling bias in this (or a similar) manner will help decision makers direct efforts and allocate resources efficiently following the observation of an apparent signal generated by such a system. Any efforts made *a priori* to reduce bias, as a fundamental aspect of signal monitoring activities, should only serve to



	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
lnRR UL	4.30	1.96	1.94	1.67	1.89	2.16	1.67	1.49	1.34	1.36	1.33	1.42	1.16	1.20
lnRR	1.10	0.00	0.51	0.41	0.69	1.01	0.69	0.63	0.51	0.59	0.60	0.69	0.50	0.54
lnRR LL	–2.10	–1.96	–0.92	–0.86	–0.51	–0.13	–0.29	–0.23	–0.32	–0.18	–0.14	–0.03	–0.17	–0.12
Paroxetine events	1	2	5	6	8	11	12	15	15	18	20	22	23	24
laTCA events	0	2	3	4	4	4	6	8	9	11	11	11	14	14



	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
lnRR UL	4.00	2.75	2.56	2.50	2.05	1.77	1.48	1.46	1.33	1.26	1.09	0.96	0.91	0.88
lnRR	1.90	1.50	1.60	1.63	1.36	1.18	1.02	1.05	0.97	0.94	0.82	0.71	0.68	0.65
lnRR LL	–0.19	0.25	0.64	0.76	0.67	0.58	0.55	0.64	0.62	0.62	0.54	0.46	0.44	0.43
Lisinopril events	7	14	25	31	40	47	69	93	115	142	172	194	216	231
ARB events	1	3	5	6	10	14	24	31	41	52	71	89	103	113



	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
lnRR UL	3.92	4.30	4.30	4.30	4.30	4.30	4.30	4.91	5.88	3.21	2.16	2.16	1.74	1.22
lnRR	0.00	1.10	1.10	1.10	1.10	1.10	1.10	1.95	3.04	1.70	1.01	1.01	0.77	0.37
lnRR LL	–3.92	–2.10	–2.10	–2.10	–2.10	–2.10	–2.10	–1.02	0.21	0.20	–0.13	–0.13	–0.19	–0.48
Cipro events	0	1	1	1	1	1	1	3	10	11	11	11	13	13
Macrolide events	0	0	0	0	0	0	0	0	0	2	4	4	6	9

Fig. 2. (**a**) Severe upper gastrointestinal bleed in paroxetine users. Event counts shown are cumulative; P5–P7 contribute to trigger of algorithm 2; similarly, P1 and P12 have point estimates at or above the threshold. (**b**) Angioedema in lisinopril initiators. Event counts shown are cumulative; algorithm 1 triggers at P2; algorithm 2 triggers at P3. (**c**) Achilles tendon rupture in ciprofloxacin initiators. Event counts shown are cumulative; algorithm 1 triggers at P9; algorithm 2 triggers at P11. **ARB** = angiotensin receptor blocker; **Cipro** = ciprofloxacin; **laTCA** = tricyclic antidepressants with low affinity for serotonin; **lnRR** = Log of Relative Risk/Rate; **lnRR UL** = Log of Upper Limit of Relative Risk/Rate; **lnRR LL** = Log of Lower Limit of Relative Risk/Rate; **P*x*** = time period *x*.

bolster stakeholders' confidence in the observation of null or confirmed signals.

For the purpose of assessing the feasibility of the system, we thought it important to focus on examples of known drug and AE pairs to contrast with single comparators that have no existing suspected association with the AE of interest. Future applications may consider multiple active comparators. Additional considerations in future applications may include issues of drug switching, drug-drug interactions and methods to deal with informative censoring. We simplified the surveillance framework by focusing on pre-specified, targeted surveillance (or 'signal refinement'). Extensions of the framework and the methods described herein are needed to explore non-pre-specified outcomes of interest (so-called all-by-all analyses). Furthermore, research is needed on the application of PS methods in the early marketing experience – a time when determinants of prescribing may rapidly evolve. The investigation and validation of these methods in the setting of targeted surveillance is critical to their application in non-pre-specified settings, where additional challenges will be encountered. The three empirical examples reported here represent all that have been tested in the system to date. As expected, signals were identified for each of the examples. The signalling timeframe in the lisinopril example was similar to that found by Brown et al.[8,39] For the ciprofloxacin example, a broader definition of the outcome that included tendonopathies and non-specific tendinitis codes did not yield a signal. Refining the codes to more accurately reflect those utilized by Seeger et al.[30] resulted in a signal, as expected, despite the referent drugs utilized in our example differing from those used by Seeger et al.,[30] and even without a more in-depth epidemiological analysis, which is a step removed from population monitoring. Finally, while the combination of PS matching and maxSPRT may result in reduced confounding, it may be of interest to compare signalling timeframes and potential for residual confounding with maxSPRT alone, or with a stratified maxSPRT analysis. Comparisons resulting from the specific scenarios explored here may not be generalizable to other drug/AE combinations. It is possible that some drug/AE comparisons may not be subject to appreciable confounding and a signalling method that does not employ some form of adjustment may indeed be appropriate under these highly specific circumstances. However, such potential for residual confounding will be highly dependent on the particular safety concern, and we would argue that in the context of signal 'strengthening' – as opposed to generation – it is generally preferable to correctly identify a signal than cause undue alarm. Further exploration of these methods in additional drug/AE examples should help investigators and stakeholders understand the circumstances under which one approach may be preferable to the other.

Conclusions

We demonstrated a proof of concept of a targeted, active safety monitoring system, incorporating a sequential, PS-matched, open cohort approach to aid in the reduction of bias in signal identification within a healthcare claims data environment through implementation of three monitoring examples. By emulating the prospective nature of active drug safety monitoring, we were able to identify the time at which signalling algorithms would (or would not) identify drug safety issues. Ongoing refinements to the processes, statistical procedures and evaluation of signal identification algorithms will enhance our overall understanding of prospective drug safety monitoring.

Acknowledgements

Conflict of interest: Drs Wilson, Wasser and Eisenberg are full-time employees of HealthCore, Inc., which is a subsidiary of WellPoint, Inc., Indianapolis, IN, USA. The company provides research consultancy service to, among other clients, major pharmaceutical, biotechnology and device manufacturers. At the time of the initial submission, Mr Wahl, Dr Daniel and Dr Rodgers were also full-time employees of HealthCore, Inc. Mr Wahl and Drs Wilson and Daniel received stock in WellPoint as a component of their compensation. Mr Wahl is now affiliated with the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. Dr Daniel is now affiliated with the Engelberg Center for Health Care Reform at The Brookings Institution,

Washington, DC, USA. Dr Bohn was a full-time employee of HealthCore, Inc., at commencement of the study; she is now an independent consultant and was paid for continued involvement in the project.

Dr Schneeweiss served as a paid clinical consultant to HealthCore, Inc., in the performance of oversight of this study and has received grants from the NIH and AHRQ. Dr Rassen has received grants and has grants pending from the NIH and AHRQ. Dr Avorn has received a grant from HealthCore, Inc., for drug safety research. Drs Gagne and Patrick have no conflicts of interest to declare that are directly relevant to the content of this study.

Authorship and ethics: Mr Wahl takes full responsibility for the integrity of this work from inception to published article. IRB approval was obtained for work described in this manuscript.

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