
Uppsala
Monitoring
Centre

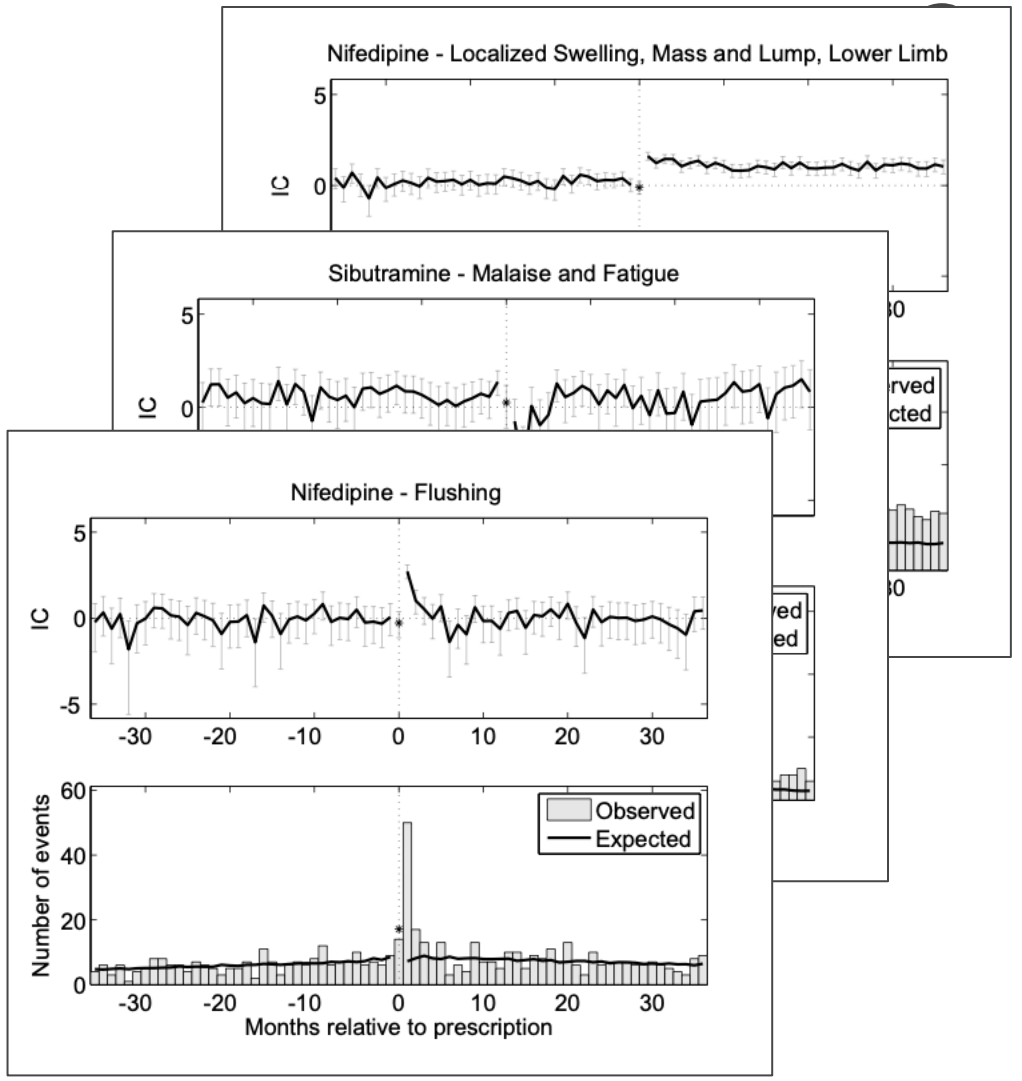
A view from the Uppsala Monitoring Centre

Niklas Norén, Chief Science Officer
Uppsala Monitoring Centre

OHDSI Sweden 2025

20 years and counting …

May 2004: celebrating completion of pilot study of pharmacovigilance signal detection in UK patient records data



OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

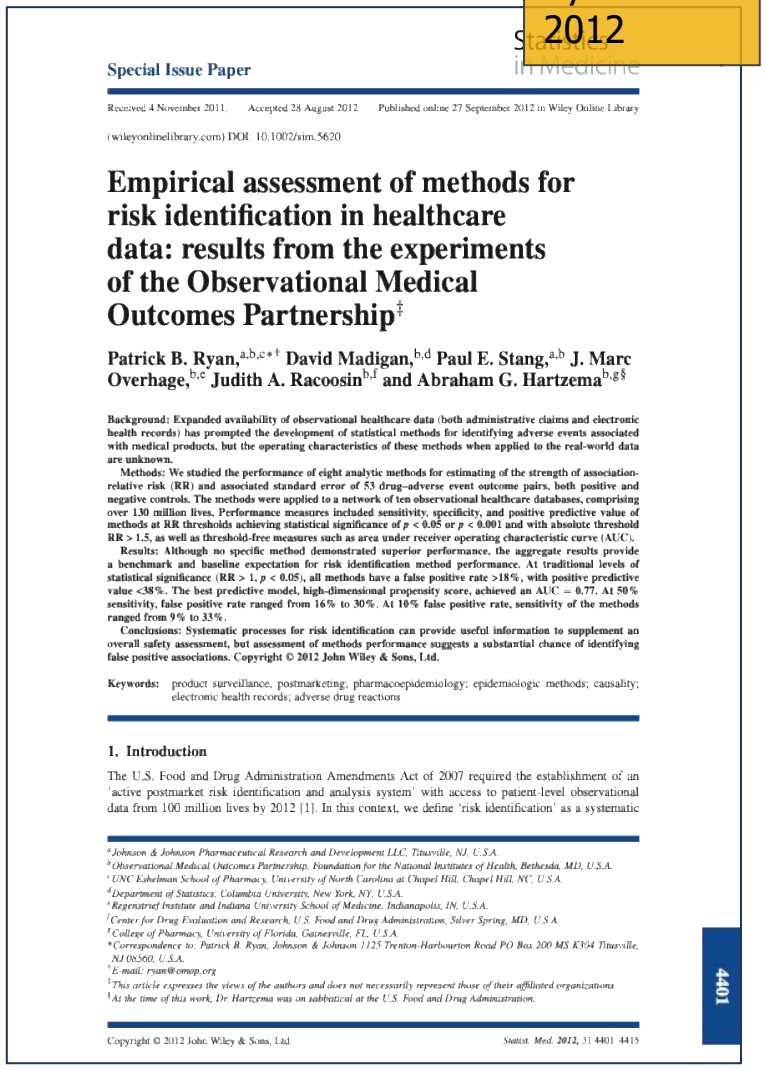
2009-2013

Evaluated use of observational healthcare databases to study the effects of medicines

Established OMOP CDM, reference sets, standardized analytics, …

UMC participated as methods partner

Ryan et al. 2012



Special Issue Paper

Received 4 November 2011, Accepted 28 August 2012, Published online 27 September 2012 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/sim.5620

Empirical assessment of methods for risk identification in healthcare data: results from the experiments of the Observational Medical Outcomes Partnership‡

Patrick B. Ryan,[a,b,c*†] David Madigan,[b,d] Paul E. Stang,[a,b] J. Marc Overhage,[b,e] Judith A. Racoosin[b,f] and Abraham G. Hartzema[b,g§]

Background: Expanded availability of observational healthcare data (both administrative claims and electronic health records) has prompted the development of statistical methods for identifying adverse events associated with medical products, but the operating characteristics of these methods when applied to the real-world data are unknown.

Methods: We studied the performance of eight analytic methods for estimating of the strength of association-relative risk (RR) and associated standard error of 53 drug–adverse event outcome pairs, both positive and negative controls. The methods were applied to a network of ten observational healthcare databases, comprising over 130 million lives. Performance measures included sensitivity, specificity, and positive predictive value of methods at RR thresholds achieving statistical significance of $p < 0.05$ or $p < 0.001$ and with absolute threshold RR > 1.5, as well as threshold-free measures such as area under receiver operating characteristic curve (AUC).

Results: Although no specific method demonstrated superior performance, the aggregate results provide a benchmark and baseline expectation for risk identification method performance. At traditional levels of statistical significance (RR > 1, $p < 0.05$), all methods have a false positive rate >18%, with positive predictive value <38%. The best predictive model, high-dimensional propensity score, achieved an AUC = 0.77. At 50% sensitivity, false positive rate ranged from 16% to 30%. At 10% false positive rate, sensitivity of the methods ranged from 9% to 33%.

Conclusions: Systematic processes for risk identification can provide useful information to supplement an overall safety assessment, but assessment of methods performance suggests a substantial chance of identifying false positive associations. Copyright © 2012 John Wiley & Sons, Ltd.

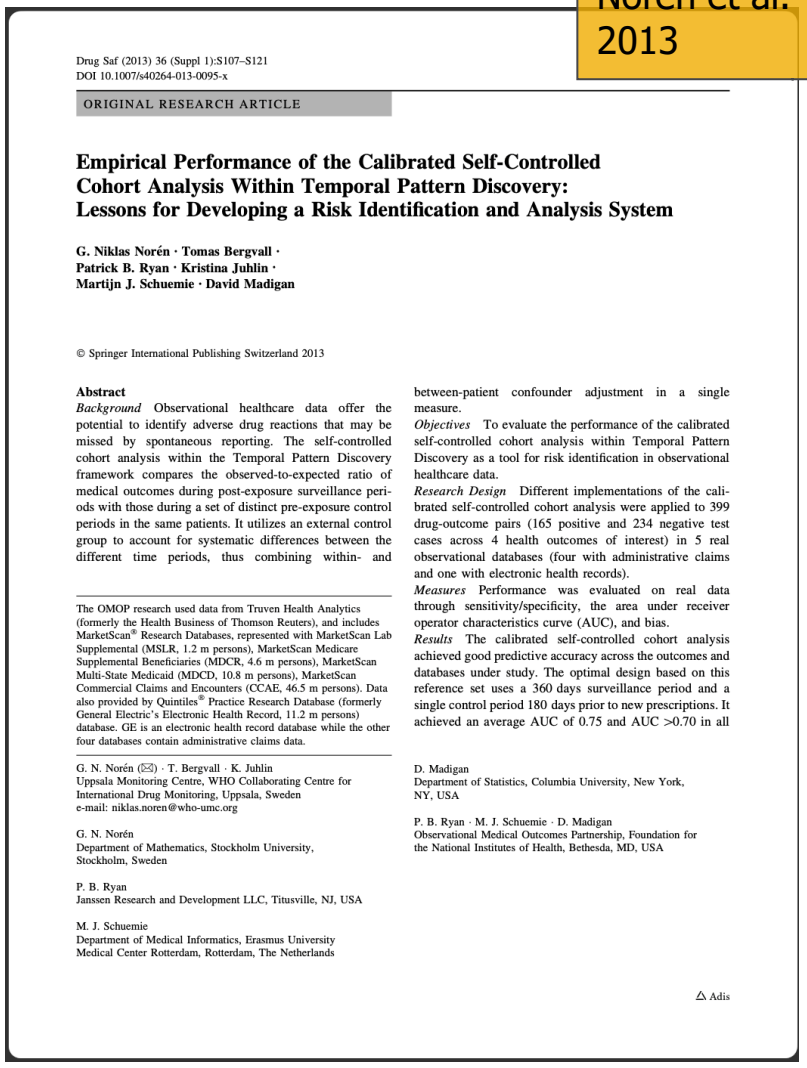
Keywords: product surveillance, postmarketing; pharmacoepidemiology; epidemiologic methods; causality; electronic health records; adverse drug reactions

1. Introduction

The U.S. Food and Drug Administration Amendments Act of 2007 required the establishment of an 'active postmarket risk identification and analysis system' with access to patient-level observational data from 100 million lives by 2012 [1]. In this context, we define 'risk identification' as a systematic

[a] *Johnson & Johnson Pharmaceutical Research and Development LLC, Titusville, NJ, U.S.A.*
[b] *Observational Medical Outcomes Partnership, Foundation for the National Institutes of Health, Bethesda, MD, U.S.A.*
[c] *UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, U.S.A.*
[d] *Department of Statistics, Columbia University, New York, NY, U.S.A.*
[e] *Regenstrief Institute and Indiana University School of Medicine, Indianapolis, IN, U.S.A.*
[f] *Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, U.S.A.*
[g] *College of Pharmacy, University of Florida, Gainesville, FL, U.S.A.*
* *Correspondence to: Patrick B. Ryan, Johnson & Johnson 1125 Trenton-Harbourton Road PO Box 200 MS K304 Titusville, NJ 08560, U.S.A.*
† *E-mail: ryan@omop.org*
‡ *This article expresses the views of the authors and does not necessarily represent those of their affiliated organizations.*
§ *At the time of this work, Dr. Hartzema was on sabbatical at the U.S. Food and Drug Administration.*

Norén et al. 2013



Drug Saf (2013) 36 (Suppl 1):S107–S121
DOI 10.1007/s40264-013-0095-x

ORIGINAL RESEARCH ARTICLE

Empirical Performance of the Calibrated Self-Controlled Cohort Analysis Within Temporal Pattern Discovery: Lessons for Developing a Risk Identification and Analysis System

G. Niklas Norén · Tomas Bergvall · Patrick B. Ryan · Kristina Juhlin · Martijn J. Schuemie · David Madigan

Abstract
Background Observational healthcare data offer the potential to identify adverse drug reactions that may be missed by spontaneous reporting. The self-controlled cohort analysis within the Temporal Pattern Discovery framework compares the observed-to-expected ratio of medical outcomes during post-exposure surveillance periods with those during a set of distinct pre-exposure control periods in the same patients. It utilizes an external control group to account for systematic differences between the different time periods, thus combining within- and between-patient confounder adjustment in a single measure.
Objectives To evaluate the performance of the calibrated self-controlled cohort analysis within Temporal Pattern Discovery as a tool for risk identification in observational healthcare data.
Research Design Different implementations of the calibrated self-controlled cohort analysis were applied to 399 drug-outcome pairs (165 positive and 234 negative test cases across 4 health outcomes of interest) in 5 real observational databases (four with administrative claims and one with electronic health records).
Measures Performance was evaluated on real data through sensitivity/specificity, the area under receiver operator characteristics curve (AUC), and bias.
Results The calibrated self-controlled cohort analysis achieved good predictive accuracy across the outcomes and databases under study. The optimal design based on this reference set uses a 360 days surveillance period and a single control period 180 days prior to new prescriptions. It achieved an average AUC of 0.75 and AUC >0.70 in all

The OMOP research used data from Truven Health Analytics (formerly the Health Business of Thomson Reuters), and includes MarketScan® Research Databases, represented with MarketScan Lab Supplemental (MSLR, 1.2 m persons), MarketScan Medicare Supplemental Beneficiaries (MDCR, 4.6 m persons), MarketScan Multi-State Medicaid (MDCD, 10.8 m persons), MarketScan Commercial Claims and Encounters (CCAE, 46.5 m persons). Data also provided by Quintiles® Practice Research Database (formerly General Electric's Electronic Health Record, 11.2 m persons) database. GE is an electronic health record database while the other four databases contain administrative claims data.

G. N. Norén (✉) · T. Bergvall · K. Juhlin
Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
e-mail: niklas.noren@who-umc.org

G. N. Norén
Department of Mathematics, Stockholm University, Stockholm, Sweden

P. B. Ryan
Janssen Research and Development LLC, Titusville, NJ, USA

M. J. Schuemie
Department of Medical Informatics, Erasmus University Medical Center Rotterdam, Rotterdam, The Netherlands

D. Madigan
Department of Statistics, Columbia University, New York, NY, USA

P. B. Ryan · M. J. Schuemie · D. Madigan
Observational Medical Outcomes Partnership, Foundation for the National Institutes of Health, Bethesda, MD, USA

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Uppsala Monitoring Centre

2014 - …

Global scope, expanded scale, continued mission

UMC active engagement primarily in the early years

Now looking to re-engage & enthusiastic about establishment of OHDSI Sweden

Boyce et al. 2014

Drug Saf (2014) 37:557–567
DOI 10.1007/s40264-014-0189-0

CURRENT OPINION

Bridging Islands of Information to Establish an Integrated Knowledge Base of Drugs and Health Outcomes of Interest

Richard D. Boyce · Patrick B. Ryan · G. Niklas Norén · Martijn J. Schuemie · Christian Reich · Jon Duke · Nicholas P. Tatonetti · Gianluca Trifirò · Rave Harpaz · J. Marc Overhage · Abraham G. Hartzema · Mark Khayter · Erica A. Voss · Christophe G. Lambert · Vojtech Huser · Michel Dumontier

Published online: 2 July 2014

Abstract The entire drug safety enterprise has a need to search, retrieve, evaluate, and synthesize scientific evidence more efficiently. This discovery and synthesis process would be greatly accelerated through access to a common framework that brings all relevant information sources together within a standardized structure. This presents an opportunity to establish an open-source community effort to develop a global knowledge base, one that brings together and standardizes all available information for all drugs and all health outcomes of interest (HOIs) from all electronic sources pertinent to drug safety. To make this vision a reality, we have established a workgroup within the Observational Health Data Sciences and Informatics (OHDSI, http://ohdsi.org) collaborative. The workgroup's mission is to develop an open-source standardized knowledge base for the effects of medical products and an efficient procedure for maintaining and expanding it. The knowledge base will make it simpler for practitioners to access, retrieve, and synthesize evidence so that they can reach a rigorous and accurate assessment of causal relationships between a given drug and HOI. Development of the knowledge base will proceed with the measureable goal of supporting an efficient and thorough evidence-based assessment of the effects of 1,000 active ingredients across 100 HOIs. This non-trivial task will result in a high-quality and generally applicable drug safety knowledge base. It will also yield a reference standard of drug–HOI pairs that will enable more advanced methodological research that empirically evaluates the performance of drug safety analysis methods.

R. D. Boyce (✉)
University of Pittsburgh, Pittsburgh, PA, USA
e-mail: rdb20@pitt.edu

P. B. Ryan · M. J. Schuemie · E. A. Voss
Janssen Research and Development, Titusville, NJ, USA

G. N. Norén
Uppsala Monitoring Centre, Uppsala, Sweden

C. Reich
AstraZeneca, Waltham, MA, USA

J. Duke
Regenstrief Institute, Indianapolis, IN, USA

N. P. Tatonetti
Columbia University, New York, NY, USA

G. Trifirò
University of Messina, Messina, Italy

Key Points

The individuals who possess the expertise to synthesize evidence on a medication's safety are hindered by numerous disconnected "islands of information"

A workgroup within the Observational Health Data Sciences and Informatics (OHDSI, http://ohdsi.org) collaborative is addressing this issue by establishing an open-source community effort to develop a global knowledge base that brings together and standardizes all available information for all drugs and all health outcomes of interest from all electronic sources pertinent to drug safety

Striving toward the goal of a generally useful knowledge base, though ambitious, is necessary for advancing the science of drug safety because it will make it simpler for practitioners to access, retrieve, and synthesize evidence so that they can reach a rigorous and accurate assessment of causal relationships between a given drug and the health outcome of interest

Adis

Hripcsak et al. 2015

MEDINFO 2015: eHealth-enabled Health
I.N. Sarkar et al. (Eds.)

doi:10.3233/978-1-61499-564-7-574

Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers

George Hripcsak[a], Jon D. Duke[b], Nigam H. Shah[c], Christian G. Reich[d], Vojtech Huser[e], Martijn J. Schuemie[f,g], Marc A. Suchard[h], Rae Woong Park[i], Ian Chi Kei Wong[j], Peter R. Rijnbeek[k], Johan van der Lei[l], Nicole Pratt[k], G. Niklas Norén[f], Yu-Chuan Li[m], Paul E. Stang[n], David Madigan[o], Patrick B. Ryan[n]

[a] *Department of Biomedical Informatics, Columbia University Medical Center, New York, NY, USA*
[b] *Regenstrief Institute, Indianapolis, IN, USA*
[c] *Center for Biomedical Informatics Research, Stanford University, CA, USA*
[d] *AstraZeneca PLC, Waltham, MA, USA*
[e] *NIH Clinical Center, Bethesda, MD, USA*
[f] *Centre for Safe Medication Practice and Research, Dept. of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong*
[g] *Janssen Research & Development, LLC, Titusville, NJ, USA*
[h] *Dept. of Biomathematics & Dept. of Human Genetics, David Geffen School of Medicine, Univ. of California, Los Angeles, CA, USA*
[i] *Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea*
[j] *Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands*
[k] *School of Pharmacy and Medical Sciences, University of South Australia, Australia*
[l] *Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden*
[m] *College of Medical Science and Technology, (CoMST), Taipei Medical University, Taipei, Taiwan*
[n] *Department of Statistics, Columbia University, New York, NY, USA*

Abstract

The vision of creating accessible, reliable clinical evidence by accessing the clinical experience of hundreds of millions of patients across the globe is a reality. Observational Health Data Sciences and Informatics (OHDSI) has built on learnings from the Observational Medical Outcomes Partnership to turn methods research and insights into a suite of applications and exploration tools that move the field closer to the ultimate goal of generating evidence about all aspects of healthcare to serve the needs of patients, clinicians and all other decision-makers around the world.

Keywords:
Health Services Research; Databases; Observation.

Introduction

Observational Health Data Sciences and Informatics (OHDSI, pronounced "Odyssey") [1] is an international collaborative whose goal is to create and apply open source data analytic solutions to a large network of health databases to improve human health and wellbeing. The OHDSI team comprises academics, industry scientists, health care providers, and regulators whose formal mission is to transform medical decision making by creating reliable scientific evidence about disease natural history, healthcare delivery, and the effects of medical interventions through large-scale analysis of observational health databases for population-level estimation and patient-level predictions [2]. Over 90 participants from around the world have joined the collaborative with a vision to access a network of one billion patients to generate evidence about all aspects of healthcare, where patients, clinicians and all other decision-makers around the world use OHDSI tools and evidence every day [3].

Methods

OHDSI grew out of the Observational Medical Outcomes Partnership (OMOP) [4], which was a public-private partnership established in the US to inform the appropriate use of observational healthcare databases for studying the effects of medical products. The five-year project developed new methods in observational research and established an observational research laboratory. At the conclusion of this five-year project, the OMOP research investigators initiated the OHDSI effort. The research laboratory moved to the Reagan-Udall Foundation for the FDA under the Innovation in Medical Evidence Development and Surveillance (IMEDS)

Table 1. Tables in the OMOP Common Data Model V5.0

Model Domain	Table Names
Standardized Clinical Data Tables	PERSON, OBSERVATION_PERIOD, SPECIMEN, DEATH, VISIT_OCCURRENCE, PROCEDURE_OCCURRENCE, DRUG_EXPOSURE, DEVICE_EXPOSURE, CONDITION_OCCURRENCE, MEASUREMENT, NOTE, OBSERVATION, FACT_RELATIONSHIP
Standardized Health System Data Tables	LOCATION, CARE_SITE, PROVIDER
Standardized Health Economics Data Tables	PAYER_PLAN_PERIOD, VISIT_COST, PROCEDURE_COST, DRUG_COST, DEVICE_COST
Standardized Derived Elements	COHORT, COHORT_ATTRIBUTE, DRUG_ERA, DOSE_ERA, CONDITION_ERA

Uppsala Monitoring Centre

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

EHDEN pharmacovigilance study-a-thon
5-9 September 2022, Uppsala

Gauffin et al. 2023

Drug Safety
https://doi.org/10.1007/s40264-023-01353-w

ORIGINAL RESEARCH ARTICLE

Supporting Pharmacovigilance Signal Validation and Prioritization with Analyses of Routinely Collected Health Data: Lessons Learned from an EHDEN Network Study

Oskar Gauffin[1] · Judith S. Brand[1] · Sara Hedfors Vidlin[1] · Daniele Sartori[1] · Suvi Asikainen[2] · Martí Català[3] · Etir Chalabi[4] · Daniel Dedman[5] · Ana Danilovic[6] · Talita Duarte-Salles[7,8] · Maria Teresa García Morales[9] · Saara Hiltunen[10] · Annika M. Jödicke[3] · Milan Lazarevic[11] · Miguel A. Mayer[12] · Jelena Miladinovic[13] · Joseph Mitchell[1] · Andrea Pistillo[7] · Juan Manuel Ramírez-Anguita[12] · Carlen Reyes[7] · Annette Rudolph[1] · Lovisa Sandberg[1] · Ruth Savage[1,14] · Martijn Schuemie[15,16] · Dimitrije Spasic[11] · Nhung T. H. Trinh[17] · Nevena Veljkovic[4,18] · Ankica Vujovic[19] · Marcel de Wilde[8] · Alem Zekarias[1] · Peter Rijnbeek[8] · Patrick Ryan[15,20] · Daniel Prieto-Alhambra[3,8] · G. Niklas Norén[1]

Accepted: 17 September 2023

Abstract

Introduction Individual case reports are the main asset in pharmacovigilance signal management. Signal validation is the first stage after signal detection and aims to determine if there is sufficient evidence to justify further assessment. Throughout signal management, a prioritization of signals is continually made. Routinely collected health data can provide relevant contextual information but are primarily used at a later stage in pharmacoepidemiological studies to assess communicated signals.

Objective The aim of this study was to examine the feasibility and utility of analysing routine health data from a multinational distributed network to support signal validation and prioritization and to reflect on key user requirements for these analyses to become an integral part of this process.

Methods Statistical signal detection was performed in VigiBase, the WHO global database of individual case safety reports, targeting generic manufacturer drugs and 16 prespecified adverse events. During a 5-day study-a-thon, signal validation and prioritization were performed using information from VigiBase, regulatory documents and the scientific literature alongside descriptive analyses of routine health data from 10 partners of the European Health Data and Evidence Network (EHDEN). Databases included in the study were from the UK, Spain, Norway, the Netherlands and Serbia, capturing records from primary care and/or hospitals.

Results Ninety-five statistical signals were subjected to signal validation, of which eight were considered for descriptive analyses in the routine health data. Design, execution and interpretation of results from these analyses took up to a few hours for each signal (of which 15–60 minutes were for execution) and informed decisions for five out of eight signals. The impact of insights from the routine health data varied and included possible alternative explanations, potential public health and clinical impact and feasibility of follow-up pharmacoepidemiological studies. Three signals were selected for signal assessment, two of these decisions were supported by insights from the routine health data. Standardization of analytical code, availability of adverse event phenotypes including bridges between different source vocabularies, and governance around the access and use of routine health data were identified as important aspects for future development.

Conclusions Analyses of routine health data from a distributed network to support signal validation and prioritization are feasible in the given time limits and can inform decision making. The cost–benefit of integrating these analyses at this stage of signal management requires further research.

1 Introduction

The detection, analysis and communication of signals that indicate a possible causal relationship between a medicine and an adverse event are key pharmacovigilance priorities. Signal management relies extensively on adverse event reports submitted by health care professionals, patients and pharmaceutical manufacturers [1, 2]. Their analysis informs most regulatory decisions related to safety signals for marketed medicinal products [3, 4]. Signal detection is the first stage of signal management and can be based on case-by-case human review of incoming adverse event reports and/or

Published online: 07 October 2023