Supporting pharmacovigilance signal validation and prioritisation 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]

Background

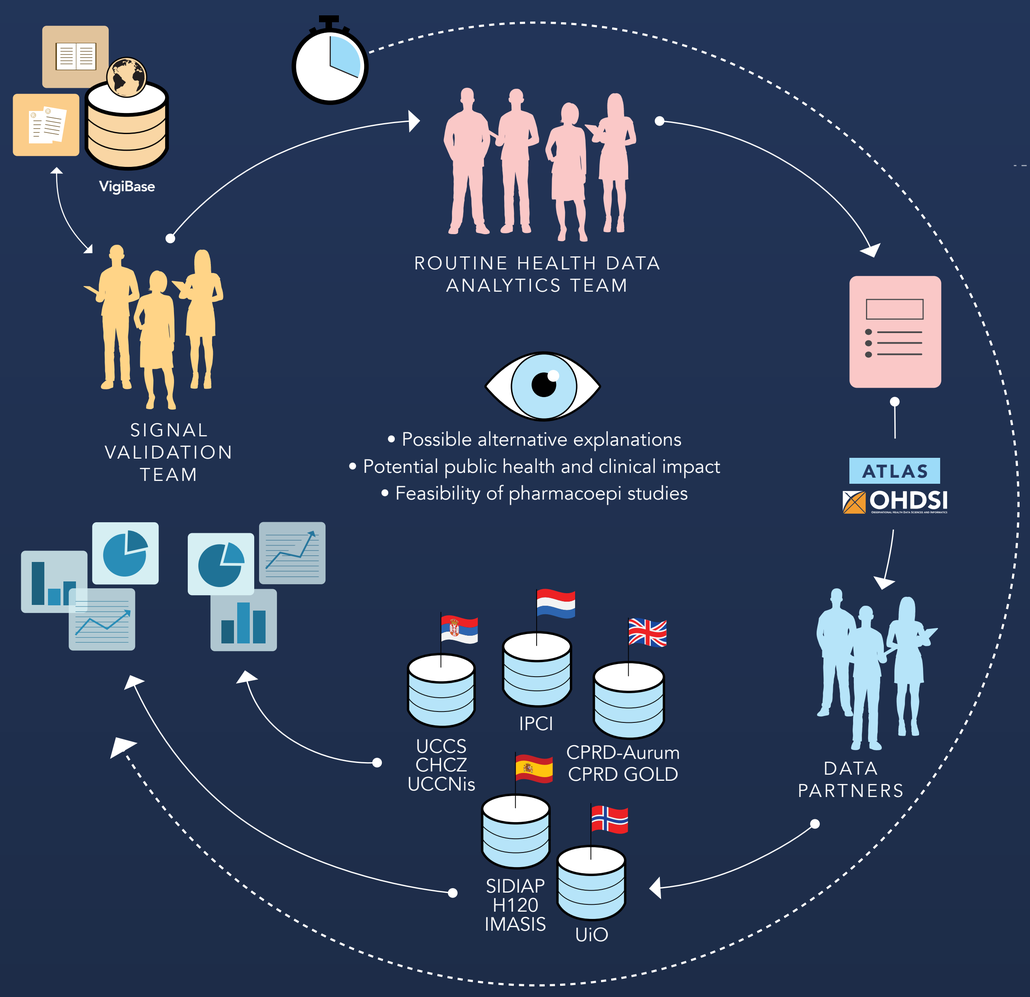
- Signal validation and prioritisation are key processes in pharmacovigilance signal management as they determine whether a detected signal merits assessment.
- These processes typically rely on insights from individual case reports, regulatory documents and the literature.

Objective:

- To examine the feasibility and utility of analysing routinely collected health data to support signal validation and prioritisation.

Methods:

- Statistical signal detection was performed in VigiBase targeting generic drugs and 16 prespecified adverse events.
- A random sample of 95 statistical signals were subjected to routine signal validation and prioritisation.
- In response to requests, descriptive analyses were conducted on routine health data from 10 data partners of the European Health Data and Evidence Network (EHDEN) to contextualise the drug, indication(s), and/or adverse event of each signal (see figure below).



MESALAZINE
Myocarditis/pericarditis

Known but large number of serious cases in VigiBase.

Insights from EHDEN:

- Rare (1–4 cases per 10,000 new users of mesalazine per year) but relatively large number of patients exposed
- Pharmacoepi study feasible with corticosteroids as active comparator and hospital/death records in larger network

DEXAMETHASONE
Acute myocardial infarction

Case series in VigiBase suggests intensified monitoring in multiple myeloma patients.

Insights from EHDEN:

- Higher incidence of acute myocardial infarction in multiple myeloma patients than in general population comparators
- <0.4% of all dexamethasone users have a history of multiple myeloma
- Too few cases for pharmacoepi analyses

Results:

- Routine health data were consulted in 8 out of 95 statistical signals and informed decisions in 5 of these (see two examples figure above).
- Several requirements for effective use of routine health data in real world signal management were identified.
  - multidisciplinary team including experts of routine health data sources
  - large and diverse data network
  - wide range of defined phenotypes for adverse events
  - effective bridges between different source vocabularies
  - pre-computation and standardisation of analytical code
  - centralised procedure for ethics approval

Conclusions:

- Analyses of multi-source routine health data are feasible in the given time limits and can provide valuable insights to validate and prioritise signals.
- The identified key user requirements highlight aspects for further development to maximise the potential of these data in signal management.

Funding information:

This activity under the European Health Data & Evidence Network (EHDEN) has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 806968. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

[1] Uppsala Monitoring Centre, Uppsala, Sweden. [2] BCB Medical Ltd, Turku, Finland. [3] Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom. [4] Heliant Ltd, Belgrade, Serbia. [5] Clinical Practice Research Datalink (CPRD), The Medicines and Healthcare Products Regulatory Agency, London, United Kingdom. [6] CHC Zvezdara, Belgrade, Serbia. [7] Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain. [8] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands. [9] Instituto de Investigación Sanitaria Hospital 12 de Octubre, CIBER de Epidemiología y Salud Pública, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain. [10] BCB Medical Ltd, Espoo, Finland. [11] Clinic for Cardiac and Transplant Surgery, University Clinical Center Nis, Serbia. [12] Hospital del Mar Medical Research Institute, Parc de Salut Mar, Barcelona, Spain. [13] Clinic for Infectious Diseases, University Clinical Center Nis, University Clinical Center Nis, Serbia. [14] Department of General Practice, University of Otago, Christchurch, New Zealand. [15] Epidemiology Department, Johnson & Johnson, Titusville, NJ, USA. [16] Department of Biostatistics, UCLA, Los Angeles, CA, USA. [17] PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway. [18] Vinca Institute of Nuclear Sciences, National Institute of the Republic of Serbia, University of Belgrade, Belgrade, Serbia. [19] Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. [20] Department of Biomedical Informatics, Columbia University Medical Center, New York, NY, USA.

Uppsala Monitoring Centre (UMC)
Box 1051, SE-751 40 Uppsala, Sweden
+46 18 65 60 60, www.who-umc.org