Signal assessment in VigiBase enhanced by EHDEN (The EHDEN Study-a-Thon)

Study protocol for the EHDEN Pharmacovigilance use case

Executive summary

Individual case safety reports (ICSRs) of suspected harm from medicines remain a major source of information to identify novel adverse drug reactions (ADRs) from marketed medicines. This study-a-thon will explore to what extent and in what ways access to a network of longitudinal observational health data (LOHD) can support and enhance the preliminary assessment of signals identified in a large database of individual case reports. Statistical signal detection will be carried out following standard operating procedures at Uppsala Monitoring Centre (UMC) using data from VigiBase, the WHO global database of individual case safety reports. The resulting set of drug-event-combinations (DECs) will then be further explored using VigiBase data, LOHD from the nascent European Health Data and Evidence Network (EHDEN), and possibly data from other parts of the world. The basis for the analyses of the LOHD will be descriptive and exploratory tools provided by the Observational Health and Data Sciences and Informatics (OHDSI) initiative and developed as part of EHDEN by the UMC. The outputs of the project will be published in the form of peer-reviewed publication(s).

Background

A medicinal product's safety profile is never fully known at the time it is approved and made available for real-world clinical use. Premarketing preclinical data and clinical trials detect many, but not all risks of harm or ADRs and important limitations of them include lack of power to detect rare adverse events, exclusion of patient groups and differences between the carefully controlled and monitored environment of a trial and the complexity and variability of clinical practice. Medicinal products are therefore monitored throughout their lifecycle for unknown ADRs and other medicine-related threats to patient safety.

In pharmacovigilance, a *signal* can be defined as "*Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action*." (CIOMS VIII).

Pharmacovigilance *signal detection* may be based on individual case reports of suspected harm from medicines, known as individual case safety reports (ICSRs). ICSRs are primarily submitted by health care professionals and patients to either pharmacovigilance centers usually located at regulatory authorities or to relevant pharmaceutical companies. They are collected in databases e. g. at regulatory authorities where signals are detected using qualitative and quantitative (statistical) methods.

Once a signal of a possible ADR in relation to a medicine is detected, a preliminary assessment is performed (in the EU referred to as signal validation). In this process, the series of individual case

reports of the signal are assessed alongside scientific and regulatory information to determine if further investigation is warranted. LOHD have so far only to a limited extent been considered at this stage but may be analyzed as part of subsequent pharmaco-epidemiological studies. Foundations for this study, of signal detection combining spontaneous and LOHD can be found in Star et al (1). A proof of concept for the present study is Chandler's publication on nintedanib-induced colitis which exemplifies the successful leverage of OHDSI Data together with ICSRs to validate a signal (2).

Aim

To complement signal detection in spontaneous case reports with aggregated LOHD from EHDEN and evaluate the usefulness of LOHD for supporting and enhancing preliminary assessment of signals.

Specific aims

Develop, test and adapt technical infrastructure to aggregate LOHD using selected parts of the OHDSI toolbox.

Enhance preliminary signal assessment using a combination of precalculated and real-time analyses of LOHD.

Qualitatively evaluate the usefulness of LOHD in the assessment of signals.

Data sources

The primary signal detection dataset is VigiBase, the WHO Global Database of ICSRs, containing data from over 140 countries participating in the WHO program for International Drug Monitoring. By April 2021, VigiBase contained > 25.5 million ICSRs and >3.5 million DECs. Medicinal products and adverse events in VigiBase are coded and analyzed using structured terminologies; medicinal products are coded according to WHO Drug Global (global substance level) which contains ATC5 level classifications (3), where products containing the same active ingredient constitute the level of analysis and the adverse events are coded to the Medical Dictionary for Regulatory Activities (MedDRA) with the level of analysis being the Preferred Term (PT) level. The most recent deduplicated version of VigiBase relative to the date of start of the study will be used during the EHDEN signal detection study-a-thon and the December 2021 workshop.

Complementary data sources for the signal assessment part of the study will consist of several such accessed via the study-a-thon (EHDEN) partners; we here referred to the sources as LOHD. These will be primarily selected from within those currently included in EHDEN and mapped to the OMOP Common Data Model. Specifically, the following data sources are currently considered: Clinical Practice Research Datalink (CPRD), Integrated Primary Care Information (IPCI). Additional external (i.e., outside EHDEN) international data sources mapped to the OMOP Common Data Model will be considered for inclusion at a later stage.

Methods

Overview of analysis

Individually tailored study designs for DEC investigations on a large scale are not feasible. Instead, we aim to undertake precalculated analyses (in VigiBase and LOHD) across a fairly wide span of DECs to identify DECs that merit further investigation for manual review by PV staff at the UMC. Analysis scripts will be executed using synthetic data (OmopCdmSynthea) before the study-a-thon, providing an opportunity to quality assure the data aggregation process. A study package will be created and shared with data partners to run on their OMOP data.

As we anticipate that the pre-calculated analyses will not be optimal in utilizing the LOHD for all DECs, once the assessment is initiated, during the study-a-thon, we will also execute specific tailored real-time ad-hoc analyses if needed to reach a further understanding on whether the detected signals are supported by the LOHD. These analyses will be carried out through ATLAS and other OHDSI analytic tools (i.e. FeatureExtraction, MethodEvaluation, CohortDiagnostics and other study design R packages available in the HADES library) particular in-depth questions have been identified during the December 2021 workshop.

Study design

Identifying DECs for further exploration

To direct manual assessment resources to DECs of potential interest, a data-driven predictive logistic regression model, vigiRank developed and used by the UMC will be used to screen the DECs and rank them (4,5). The predictive model is based on several aspects of disproportionality, report quality and recency, geographic spread and presence of case narratives in VigiBase; empirical evaluation has shown increased predictive performance compared to traditional disproportionality analysis (4). Primary signal detection for the study-a-thon will be focused at generic drugs and a fairly broad class of adverse events likely to be captured in available LOHD and excluding events that are not suited for temporal association analyses. For each of the DECs selected for manual assessment regulatory information (e.g.: relevant Summaries of Products Characteristics and, where available, Risk Management Plans) will be consulted and the series of ICSR of the DEC in VigiBase preliminary assessed: detected DECs for which the corresponding ADRs are labelled will be dismissed. For remaining DECs, LOHD will be considered alongside UMC's standard practice preliminary assessment of the case series. If a DEC is still considered relevant to pursue clinically, in-depth assessment will be attempted during the study-a-thon. Details of the DEC identification process for the December 2021 workshop can be found in Appendix 1.

Preliminary assessment of DECs via LOHD

The methods applied to the LOHD will initially be open-ended and descriptive and exploratory in nature. Descriptive tables, visualizations and hypothesis-generating aggregations will be a core component, but we will also consider additional analyses using other study designs at a later stage (i.e., active comparator and self-controlled case series) to enhance causal assessment of promising signals following this first screen of analyses. Apart from this, more in-depth ISCR assessment of those signals will be attempted by UMC staff.

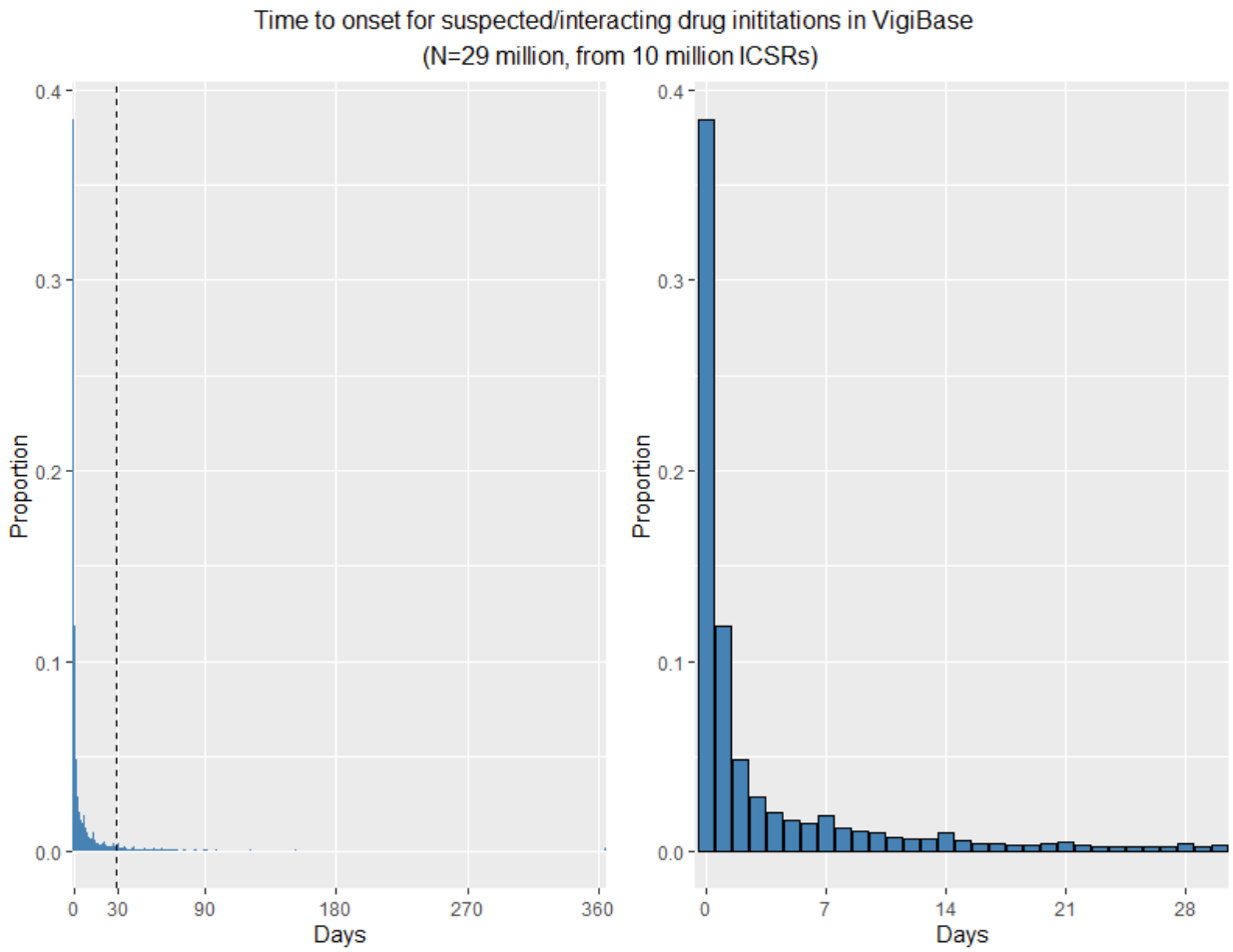

Figure X: Reported Time to onset for suspected or interacting medicinal product initiations and adverse events with complete dates. ICSR = Individual Case Safety Report.

A known limitation of signal detection in ICSRs is the difficulty in detecting ADRs with long latency. To match the nature of ICSR data in VigiBase, the risk window for LOHD analyses will be set to 30 days, but an extension of this window to 90 days will be considered depending on the outcome of the December 2021 workshop.

Study populations

For each DEC, the study population will consist of new users of the target drug (i.e., the "target drug cohort") and a comparator group of new users of any other drug (i.e., the "comparator drug cohort"). The comparator drug cohort has been compiled by randomly sampling one drug per individual. The index date in both cohorts will be defined as the date of first drug initiation, and we will only consider individuals with at least 13 months of database history for inclusion (to ensure a sufficiently long observation period for capturing first time use). This study population will serve as input for temporal association and descriptive analyses. To address imbalances in age, sex, and calendar period at drug initiation between the two cohorts, we will consider matching the comparator drug cohort to the target drug cohort on these variables (1:10 ratio) (not the focus of the December 2021 workshop).

Outcomes

Outcome definitions will be DEC and analysis specific. For temporal association analyses the outcome will be defined as any occurrence of the adverse event within a 3 yrs window before and/or after the index date. For descriptive analyses, the outcome will be defined as first occurrence of the event within 30 days following the index date. Of note, individuals with the outcome prior to the index date will not be excluded from the study population in any of these analyses.

Covariates

We will consider the following covariates for our analyses: demographics (age, sex), pre-existing medical conditions and co-medications. Pre-existing medical conditions will be set to any time prior to (and including) the index date. The time window for co-medications will be set to 180 days prior to and including the index date. For descriptive purposes, we will further consider variables related to the target drug and event of each DEC: time elapsed from target drug initiation to event occurrence and treatment duration.

Analyses

Temporal association analyses

For each DEC, temporal associations between the drug of interest and adverse event will be visualized using a chronograph, its core methodology has been published elsewhere (6). In brief, the chronograph focuses on the target drug cohort and explores variation over time in the recording of the adverse event relative to the date of drug initiation and it compares this number of observed events to an expected value based on comparator drug data in each time window. The chronograph consists of two parts: 1). a bottom panel emphasizing absolute differences of observed and expected counts; and 2). a top panel emphasizing relative differences expressed as the ratio of these two values (i.e observed to expected ratio) subjected to statistical shrinkage and presented on a logarithmic scale (referred to as the information component (IC). See also Figure 1 for an example.

For assessing possible ADRs, we focus on shifts in the IC around the index date, in particular asymmetries where the IC rises sharply shortly after drug initiation. Other more distant time windows of the chronograph provide additional valuable information. For instance, the window to the far left represents the experience of individuals prior to exposure to the target and resulting baseline risk to develop the event compared to individuals treated with the comparator drug. The window on the far right provides insight into whether ICs remain elevated long-term after drug initiation.

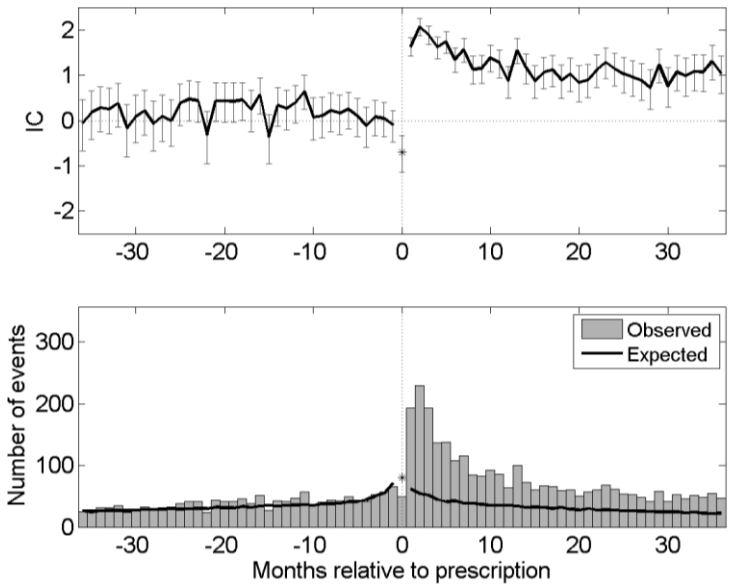

Figure 1. IC = information component. Example of a chronograph representation of the temporal association between the first prescription of a drug and registration of an adverse event in LOHD. The top panel provides credibility intervals where values above 0 indicates significant disproportionality, while the bottom panel displays the underlying observed and expected counts.

Descriptive analyses

Descriptive analyses will be undertaken to determine the frequency of the event in the target and comparator drug cohort and to support the exploration of possible alternative explanations to an observed temporal association (confounding or other risk factors). For each DEC, we will compute descriptive statistics of covariates (demographics, comorbid conditions, previous healthcare system interactions and co-medications) for the target drug and comparator drug cohort as well as subsets of these two cohorts with the event of interest. We will then compare descriptive statistics across these four sets of data to increase our understanding of determinants associated with drug exposure and the event of interest (to evaluate potential confounding and protopathic bias). In daily practice, reasons to prescribe (or not to prescribe) a target drug are per definition associated with exposure to that drug, unless allocation to a drug is a random process (which is not the case in LOHD). Therefore, the presence or absence of the relationship between the reasons to prescribe the target drug and the event determines the potential for confounding.

Evaluation of the usefulness of LOHD in signal assessment

During the study-a-thon, assessments of the usefulness of LOHD for each DEC will follow a structured, anonymous questionnaire to be captured in an electronic form. Its elements will correspond to the items below:

- What type of information does the LOHD provide?
    - Support for a temporal association between the and adverse event
    - Refutation of a temporal association between the target and adverse event
    - Identification of alternative explanations for the signal identified (possible confounders and/or other risk factors)
    - Contextual information related to medicinal product utilization (e.g. number of prescriptions)
    - Contextual information related to the adverse event (e.g. incident/prevalent cases)

- What limitations do the LOHD have that may limit their value to the analysis of detected signals?
    - Suspected inaccurate mapping of medicinal products or adverse events between structured terminologies and other types of information bias related to different granularity of the data sources available.
    - Suspected lack or low number of recorded prescriptions of the medicinal product in the available data.
    - Suspected lack or low number of recorded occurrences of the adverse event in the available data
    - Although the data sources contain relevant data, more tailored analyses addressing confounding and other biases for each DEC would be required (see Appendix 2 for proposed additional analyses).

Data confidentiality

In VigiBase, as data is de-identified before entering the database, data confidentiality is generally not an issue.

Regarding the LOHD, the data will be delivered, analysed and presented on an aggregated level preventing any confidentiality breach.

No linkage of individual patients in VigiBase and LOHD will be performed. National pharmacovigilance centres sharing ICSRs to VigiBase are instructed to not include patient identifiers such as personal identification numbers, patient names, addresses in free text fields. Data partners providing LOHD will only share data in aggregated form, without any patient identifiers. Even if data partners would contribute with data sources containing personal identifiers, such details would not be aggregated by the scripts and will never leave their original allocation.

De-identified patient level VigiBase data will be available during the study-a-thon for the participants and will be stored for reproducibility according to standard operating procedures at UMC. Aggregated LOHD will (if data licenses allow) be stored on-site at UMC no more than one month in advance of the study-a-thon, for display during the study-a-thon and communication of assessed signals, e.g.: in scientific publications. Aggregated LOHD will for the purpose of reproducibility be stored at UMC when possible, or at least by the data partner depending on the data license.

Limitations

The origin, coverage and content of different LOHD varies e.g.: coverage of either only primary care or secondary care, which will affect the ability to generalize the conclusions of the study. The scope of statistical signal detection in VigiBase is, if applicable, targeted at medicinal products and adverse events that are likely to be covered by the LOHD considered in the study (e.g.: in- or out-patient data) and this must be accounted for in the discussion.

The structured qualitative evaluation targets potential benefits based on previous experiences of signal detection using ICSRs. As those previous experiences might be targeted towards specific medicinal products, adverse events or patient populations, the generalizability of the outcomes of this study-a-thon may be affected.

References

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2. Chandler RE. Nintedanib and ischemic colitis: Signal assessment with the integrated use of two types of real-world evidence, spontaneous reports of suspected adverse drug reactions, and observational data from large health-care databases. Pharmacoepidemiol Drug Saf. 2020 Aug;29(8):951–7.

3. Lagerlund O, Strese S, Fladvad M, Lindquist M. WHODrug: A Global, Validated and Updated Dictionary for Medicinal Information. Ther Innov Regul Sci [Internet]. 2020 Feb 20 [cited 2020 May 28]; Available from: http://link.springer.com/10.1007/s43441-020-00130-6

4. Caster O, Juhlin K, Watson S, Norén GN. Improved Statistical Signal Detection in Pharmacovigilance by Combining Multiple Strength-of-Evidence Aspects in vigiRank: Retrospective Evaluation against Emerging Safety Signals. Drug Saf. 2014 Aug;37(8):617–28.

5. Caster O, Sandberg L, Bergvall T, Watson S, Norén GN. vigiRank for statistical signal detection in pharmacovigilance: First results from prospective real-world use. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):1006–10.

6. Norén GN, Hopstadius J, Bate A, Star K, Edwards IR. Temporal pattern discovery in longitudinal electronic patient records. Data Min Knowl Discov. 2010 May 1;20(3):361–87.

Appendix 1. Identification of DECs for December 2021 workshop.

For the December 2021 workshop we will use DECs from a 2018 sprint carried out at the UMC (n ~ 30 000 DECs), from which we selected the top-ranked DECs by sorting DECs in order of descending vigiRank score. The selection of DECs was narrowed to those with successful mapping to standard drug (RxNorm) and event (SNOMED) concepts of the Common Data Model (CDM). From this list, one pharmacist excluded DECs with non-generic drugs as agreed with the data partners (a drug was considered a generic when patent first expired, regardless of region), DECs with biosimilars, DECs with event terms not likely to be diagnosed in primary care setting (e.g. terms related to diagnostic or lab procedures, conditions requiring ascertainment through biopsy or imaging). Given the focus on temporal association analyses, we further excluded DECs with events related to birth or pregnancy. We then reviewed the United Kingdom/European Union (1) and United States (2,3) summaries of product characteristics for all the eligible DECs and discarded those for which ADRs were an exact match was present in both sources. Where a label was unavailable because the drug was withdrawn from market or never approved in both of these regions, the first of the following country sources to have a label was consulted instead: Canada (4), Italy (5), Malaysia (6), Switzerland (7). This procedure led to the identification of ~ 100 DECs meriting further investigation in LOHD that will be used as input for the December 2021 workshop.

1. https://www.medicines.org.uk/emc/
2. https://www.accessdata.fda.gov/scripts/cder/daf/
3. https://dailymed.nlm.nih.gov/dailymed/
4. https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
5. https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/cerca-per-principio-attivo
6. https://www.mims.com/
7. https://www.swissmedicinfo.ch/Accept.aspx?ReturnUrl=%2f

Appendix 2. Proposed additional analyses.

In addition to the pre-specified analyses described above, we consider undertaking more tailored analyses for each DEC to further enhance the signal detection process. For instance, temporal association analyses can be customized to better address confounding if cohort size and event counts permit. This could be achieved by narrowing down the comparator drug cohort to individuals having the same indication as individuals receiving the target drug, and possibly propensity score (PS) matching to address residual confounding by other measured covariates in LOHD. We also consider using other analytic tools available in the OHDSI toolbox (including MethodEvaluation (negative controls) and alternative study design R packages available in the HADES library) to better address confounding, bias and measurement error. Ultimately, this type of framework where results will be compared across different types of study designs and methods each having different inherent limitations and key sources of bias will facilitate the causal assessment of potential safety signals.