Validation of statistical signal detection procedures in eudravigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling.

First published: 20/10/2010

Last updated: 19/07/2016

Study Finalised

Administrative details

EU PAS number

EUPAS1594

Study ID

14160

DARWIN EU® study

No

Study countries

☐ United Kingdom

Study description

OBJECTIVE: To evaluate whether statistical signal detection in spontaneous reporting data can lead to earlier detection of drug safety problems and to assess the additional regulatory work entailed. METHODS: Using the EudraVigilance post-authorization module (EVPM), a screening procedure based on the proportional reporting ratio (PRR) was applied retrospectively to examine if regulatory investigations concerning ADRs could have been initiated earlier than occurred in practice. During the same time period (Sep03 - Mar07), the number of PRR-based signals of disproportionate reporting (SDR) that arose in a predefined set of products was calculated and evaluated to determine the number requiring investigation. RESULTS: In 191 chemically different products, 532 adverse reactions were added to the summary of product characteristics during the study period. Of these, 405 were designated as important medical events (IMEs) based on a comprehensive predefined list. Of the IMEs, 217 (53.6%) were identified earlier by the statistical screening technique, 79 (19.6%) were detected after the date at which they were raised by standard pharmacovigilance (PhV) methods and 109 (26.9%) were not signalled during the study period. 1561 SDRs requiring further evaluation were detected during the study period, giving a ratio of 7.2 assessments for each signal pre-empted. The mean delay between the discovery of signals using the statistical methods in the EVPM and established methods in the 217 cases detected earlier was 2.45 years. A review resulted in clear explanation for why the statistical method had not pre-empted detection in all but 77 of 188 cases. CONCLUSIONS: The form of statistical signal detection tested in this study can provide significant early warning in a large proportion of drug safety problems, however, it cannot detect all safety issues more quickly than other PhV processes and hence it should be used in addition to, rather than as an alternative to, established methods.

Study status

Finalised

Research institutions and networks

Institutions

European Medicines Agency (EMA)

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Contact details

Study institution contact

Jim Slattery Jim.Slattery@ema.europa.eu

Study contact

Jim.Slattery@ema.europa.eu

Primary lead investigator

Yolanda Alvarez

Primary lead investigator

Study timelines

Date when funding contract was signed

Actual: 01/12/2006

Study start date

Actual: 05/03/2007

Date of final study report
Actual: 01/06/2010

Sources of funding

- EMA

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Other

Study topic, other:

Signal detection procedure

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

To evaluate whether statistical signal detection in spontaneous reporting data can lead to earlier detection of drug safety problems and to assess the additional regulatory work entailed.

Study Design

Non-interventional study design

Cohort

Cross-sectional

Population studied

Short description of the study population

N/A

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)

- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Special population of interest

Renal impaired

Hepatic impaired

Immunocompromised

Pregnant women

Estimated number of subjects

0

Study design details

Outcomes

To quantify the benefit that can be obtained by adding PRR signal detection to established pharmacovigilance methods. It means not only whether PRR methods can detect ADRs but with whether they can detect ADRs earlier than the other methods. The risk or regulatory resource cost of adopting the PRR procedure. It means the effort involved in assessing the many other SDRs that will arise but prove to be unrelated to any pharmacological effect of the product.

Data analysis plan

The distribution of delays between SDRs and signals from other pharmacovigilance methods is presented as Kaplan-Meier curves and confidence intervals (CIs) for statistics based on such curves using standard techniques. CIs on proportions assume binomial distributions. The rule used to define an signals of disproportionate reporting (SDR) is that the lower bound of the central 95% CI on the PRR is >1, and three or more reports have been received naming the relevant product and adverse event.

Documents

Study publications

Alvarez Y, Hidalgo A, Maignen F, Slattery J. Validation of statistical signal d...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Spontaneous reports of suspected adverse drug reactions

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No