24 April 2017
EMA/699377/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Measuring the Impact of Medicines Regulatory Interventions – Systematic Review and Methodological Considerations

Protocol for a Systematic Literature Review

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1. Study information

Title	Measuring the impact of medicines regulatory interventions – systematic review and methodological considerations
Protocol version identifier	1.1
Date of last version of the protocol	24 April 2017
EU PAS Register No:	EUPAS21337
Active substance	Multiple (systematic review)
Medicinal product(s):	Multiple (systematic review)
Study initiator	European Medicines Agency (EMA)
Research question and objectives	This study is a key deliverable of the ENCePP Special Interest Group (SIG) Impact work plan to support the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities (EMA/790863/2015). The aim of this systematic review of the literature is a descriptive overview of the study designs and analytical methods used for measuring the impact of pharmacovigilance regulatory actions taken to safeguard public health. The study has the following objectives: • Perform a systematic review of published studies evaluating the impact of pharmacovigilance regulatory interventions worldwide; • Describe the study design used to evaluate the impact of pharmacovigilance regulatory interventions; • Describe the analytical approach used to determine whether impact occurred, including the type of outcome measures;
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2. List of Abbreviations

DHPC Dear Healthcare Professional Communication

EMA European Medicines Agency

ENCePP European Network of Centres of Pharmacovigilance and Pharmacoepidemiology

EU European Union

FDA United States Food and Drug Administration

GVP Good Pharmacovigilance Practices

MeSH Medical Subject Heading

NCA National Competent Authority

PRAC Pharmacovigilance Risk Assessment Committee

US United States

3. Responsible parties

Project lead and corresponding author: Thomas Goedecke (EMA)

Literature review and data extraction: Alexandra Pacurariu, Daniel Morales, Thomas Goedecke (EMA)

Project sign-off: Xavier Kurz (EMA)

4. Rationale and background

This study is a key deliverable of the ENCePP Special Interest Group Impact work plan to support the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities (EMA/790863/2015). The evaluation of the public health impact of regulatory interventions is paramount to continuously develop and improve pharmacovigilance systems but there is currently no common methodological approach to guide this evaluation.

The aim of this systematic review of the literature is a descriptive overview of the study designs and analytical methods used for measuring the impact of pharmacovigilance regulatory actions taken to safeguard public health.

5. Research question and objectives

The study has the following primary objectives:

- Perform a systematic review of published studies evaluating the impact of pharmacovigilance regulatory interventions worldwide;
- Describe the study design used to evaluate the impact of pharmacovigilance regulatory interventions;
- Describe the analytical approach used to determine whether impact occurred, including the type of outcome measures;

6. Methods

6.1. Study design

This descriptive study is a systematic review of published articles of the peer-reviewed scientific literature.

6.2. Setting and data sources

Bibliographical database searches in MEDLINE and EMBASE will be performed. Key words cited in the known reference articles will be combined with additional terms to construct a search query to generate a representative sample of articles and methodologies applied to impact research. The terms for the electronic search strategy in MEDLINE and EMBASE described the Annex.

The electronic search will be further supplemented with hand searching of references from systematic reviews identified in the electronic search, including known published articles in the area of impact research from international regulatory networks in pharmacovigilance (EU, US, Canada and Japan).

6.3. Inclusion and exclusion criteria

All articles in English language published up to 31 March 2017 evaluating the impact of pharmacovigilance regulatory interventions for medicines for human use will be included.

A regulatory intervention is defined as any regulatory action taken by an EU or non-EU competent authority to safeguard public health in relation to the use of medicinal products, including label changes, risk communication to the public or healthcare providers, product-specific additional risk minimisation measures (defined in GVP module XVI on Risk minimisation measures: selection of tools and effectiveness indicators), withdrawal or suspension of a marketing authorisation.

Typical regulatory interventions that would qualify for inclusion include DHPC, black box warning (US only), product information update, regulatory safety communication (e.g., guideline update, public health advisory communication, safety communication on NCA websites), other additional risk minimisation measures (e.g. medication guide, pregnancy prevention programme, controlled distribution), product suspension/withdrawal, and others (e.g. change in legal status, pack-size restriction).

Duplicates, abstracts, letters to editors, commentaries and articles analysing the impact health policy changes and studies investigating the impact of pharmacovigilance processes were excluded. Articles where relevant information for the descriptive analysis could not be retrieved were also excluded.

6.4. Selection process

Eligible articles will be screened by title and abstract by one of three reviewers (TG, AP, DM) with experience in regulatory science and pharmacoepidemiology.

In a second stage, the eligibility of articles will be evaluated based on a full text review performed individually by each reviewer. Each reviewer will be randomly allocated approximately the same number of articles for full text review.

In case of disagreement on the eligibility, discussions between the three reviewers will be held to reach consensus.

6.5. Data extraction and variables

A standardised data extraction form was created a priori. For each of the following variables mutually exclusive categories will be created: regulatory intervention, data source, study design, analytical method and outcome measure. The categories for each variable are labelled systematically and selected from drop-down lists in the data extraction form. All other fields in the data extraction form are free text fields.

The following information will be extracted from each eligible article into the data extraction form:

- Reference (first author, year of publication, abbreviated title)
- Limitations (if reported)
- Regulatory intervention
    - Product information update (restriction of indication, posology, warning, contraindication, adverse reaction etc.) [PI Update]
    - Regulatory safety communication (FDA Advisory, NCA Safety Communication) [Reg. Safety Comm.]
    - FDA Black box warning [FDA BB Warning]
    - Direct Healthcare Professional Communication [DHPC]
    - Other additional risk minimisation (educational materials, patient alert card etc.) for HCPs/patients [Other aRMM]
    - Withdrawal/suspension [Withdrawal/susp.]
    - Other [Other]
- Regulatory intervention year (date)
- Data source
    - Electronic healthcare (medical) records database [eHR (medical) DB]
    - Administrative (claims) records (including prescribing/dispensing records [Claims DB]
    - Spontaneous reports (ICSR) database (e.g. EudraVigilance, VigiBase, AERS, poison control centre, etc.) [Spont. Report. DB]
    - Registries (exposure or disease) [Registry]
    - Other [Other]
- Country(ies) where the study is conducted
- Study design
    - Randomised controlled trial [RCT]
    - Analytical retrospective cohort study (compares exposed and unexposed) [Cohort study]
    - Quasi-experimental (Controlled/Uncontrolled) Before/after design with single cross-sectional measure before and after the intervention [B/A cross sectional]
    - Quasi-experimental (Controlled/Uncontrolled) Before/after design with time series (repeated cross-sectional measures) [B/A time series]
    - Descriptive cross-sectional study (survey or database study) [Cross-sectional single time point]
    - Other (e.g. ecological study) [Other]
- Analytical method
    - Descriptive statistics (rate, proportion, mean (SD), median, incidence etc.) [Descript. stats]
    - Descriptive statistics with significance test (e.g. t-test, X2, etc.) [Descript. Stats signif.]
    - Poisson regression [Poisson R]
    - Logistic regression [Logistic R]
    - Interrupted Time Series regression analyses [ITS]

    - Joinpoint regression [Joinpoint R]
    - Other [Other]
- Sample size and target population
- Main outcome measure(s)
    - Knowledge/awareness/behaviour changes in clinical practice, including patient monitoring [Knowl. Behav. Pract.]
    - Drug use (prescription, dispensing) [Drug use]
    - Health outcomes (ADR, morbidity, mortality, risk etc.) [Health outcomes]
    - Other [Other]
- Key findings: summary of the results from abstract and indication if a significant effect or no-significant effect of the regulatory intervention could be measured
- Drug or therapeutic class (ATC Code)

For variables where multiple categories could apply the category with the highest relevance for measuring the public health impact will be selected.

6.6. Data management

Data extraction will be performed from eligible articles in PDF format into Microsoft EXCEL. Quality checks of data entry will be performed by co-authors.

6.7. Data analysis

Descriptive analysis will be performed (totals and percentage) for each of the extracted variables.

7. Limitations

Not all impact research may have been published in scientific journals given that the majority of impact research is communicated within regulatory procedures

Unpublished research will not be captured by our search strategy and therefore not included in the review. There is a risk of publication bias to be acknowledged, i.e. there is a likelihood that only studies with positive findings (i.e. positive health outcomes) will be published.

Articles might also be missed with the search strategy due to a lack of standardised reporting of study designs, analytical methods and outcomes. As a remedy the search strategy will be supplemented with references from published review articles and known in-house literature.

8. Plans for communicating study results

The study results including the final study protocol will be published in the EUPAS Register. A manuscript of the study results will be submitted for publication to a peer-reviewed journal.

10. Annex

MEDLINE search strategy using MeSH terms:

"Humans" AND English[Language] AND ("Pharmacovigilance" OR "Drug-Related Side Effects and Adverse Reactions" OR "Prescription Drugs/adverse effects") AND (Regulatory policy OR Policy evaluation OR Impact research OR Outcomes research OR Impact OR Health behaviour OR Clinical behaviour OR Population impact OR Public health OR Drug legislation OR Risk assessment OR "Health Knowledge, Attitudes, Practice") AND ("Outcome Assessment (Health Care)/*methods" OR "Practice Patterns, Physicians'/*trends" OR "Product Surveillance, Postmarketing/*methods/statistics & numerical data" OR "Risk Assessment /standards" OR "Time Factors" OR "Risk Assessment/methods" OR Drug utilisation OR Drug usage OR Analytic method OR Time series OR Time trends OR Segmented regression OR Trends OR survey OR questionnaire OR switching pattern OR Pre-post OR Cross-sectional OR before after OR Registry) and (risk minimization intervention OR risk minimization measure OR risk minimisation measure OR regulatory intervention OR regulatory action OR label change OR warning OR contraindication OR suspension OR withdrawal OR restriction OR patient education OR health care professional education prescriber education OR patient alert card OR patient registry OR medication guide OR restricted distribution OR laboratory monitoring OR drug monitoring OR dear (health care or healthcare) professional OR dear doctor letter OR black box warning OR black triangle).

EMBASE search strategy:

('human' OR 'humans' OR 'human'/exp OR 'm?n' OR 'wom?n' OR 'child' OR 'boy' OR 'girl' AND ('drug surveillance program'/mj OR 'drug surveillance program' OR 'pharmacovigilance'/mj OR 'pharmacovigilance') AND ('regulatory policy' OR 'policy evaluation' OR 'impact research' OR 'outcomes research'/mj OR 'outcomes research' OR 'impact'/mj OR 'impact' OR 'health behavior'/mj OR 'health behaviour' OR 'health behavior' OR 'clinical behaviour' OR 'clinical behavior' OR 'population impact' OR 'public health'/mj OR 'public health' OR 'drug legislation'/mj OR 'drug legislation' OR 'risk assessment'/mj OR 'risk assessment' OR 'attitude to health'/mj OR 'attitude to health' OR 'health knowledge') AND ('postmarketing surveillance'/mj OR 'postmarketing surveillance' OR ('product surveillance' NEAR/3 ('method*' OR 'statistic*' OR 'numerical data') OR 'risk assessment'/mj AND ('procedures'/mj OR 'standards'/mj)) OR 'risk assessment' NEAR/3 ('method*' OR 'procedure*' OR 'standard*') OR 'time factor'/mj OR 'time factor*' OR 'drug utilization'/mj OR 'drug utilization' OR 'drug use'/mj OR 'drug use' OR 'drug usage'/mj OR 'drug usage' OR 'analytic method'/mj OR 'analytic method*' OR 'time series analysis'/mj OR 'time series' OR 'time trend'/mj OR 'time trend*' OR 'regression analysis'/mj OR 'regression analysis' OR 'segmented regression' OR 'trends'/mj OR 'trend*' OR 'survey'/mj OR 'survey*' OR 'questionnaire'/mj OR 'questionnaire*' OR 'switching pattern*' OR 'pre-post' OR 'cross-sectional' OR 'before after' OR 'register'/mj OR 'register' OR 'registry'/mj OR 'registry') AND ('risk minimization intervention*' OR 'risk minimization measure*' OR 'risk minimisation measure*' OR 'regulatory intervention*' OR 'regulatory action*' OR 'label change*' OR 'warning'/mj OR 'warning*' OR 'warning signal'/mj OR 'warning signal*' OR 'contraindication' OR 'suspension'/mj OR 'suspension*' OR 'withdrawal'/mj OR 'withdrawal*' OR 'patient education'/mj OR 'patient education' OR 'healthcare professional education' OR 'prescriber education' OR 'patient alert card' OR 'patient registry'/mj OR 'patient registr*' OR 'medication guide' OR 'laboratory monitoring' OR 'drug monitoring'/mj OR 'drug monitoring' OR 'dear healthcare professional' OR 'dear health care professional' OR 'dear doctor letter' OR 'black box warning'/mj OR 'black box warning*' OR 'black triangle').