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Case-level causality assessment methodologies, their application, utility, and limitations in determining possible adverse drug reaction: A Scoping review protocol

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ADMINISTRATIVE INFORMATION

Support - Unconditional grants.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 January 2024 and was last updated on 26 January 2024.

INTRODUCTION

Review question / Objective What causality assessment scales/tools/instruments/methods are being utilised to assess potential adverse drug reactions (ADRs) in patients (irrespective of age, sex, or pregnancy status) exposed to a licenced medicinal product (prescription or over the counter), vaccine or a herbal or traditional therapy at the individual case level? What are the applications, utility, and limitations of each method? What recommendations are there for further research if applicable?

Background The International Working Group (IWG) on New Developments in Pharmacovigilance (PV) have a mission to progress pharmacovigilance methodologies and promote the safe and effective use of medicines and vaccines, thereby protecting patients. The group aims to advance existing methodologies used in the detection, monitoring, and analysis of safety data in PV, and to communicate best practice proposals to support decision making in healthcare. The IWG identifies areas which require a review of current processes or methodological research and aims to communicate their output through reviewed publications, reports, and the presentation of findings at relevant conferences and scientific meetings. The group are currently reviewing the area of causal inference in PV.

Rationale PV is a dynamic field and new case-level causality assessment methodologies, which require review, are continuously in development. The IWGs scoping review aims to build on previous work in this area, by reviewing published case-level causality methods, including those used to evaluate specific outcomes of interest. The review will include an appraisal of each methods' strengths and weaknesses, as derived from the authors and also objectively by the reviewer based on a set of evaluation questions which will be

agreed upon a-priori. The aim of the IWGs scoping review is not to recommend one assessment scale or tool but provide an overview and characterisation of the existing methods of case level assessment tools and to consider areas of potential further research based on the findings.

METHODS

Strategy of data synthesis Embase and MEDLINE will be systematically searched for review studies. The search are:
((“algorithms” OR algorithm* OR “bayes theorem” OR “bayes” AND “theorem” OR “probability theory” OR “probability” AND “theory” OR “logistics” OR “global introspection” OR “expert judgement” OR “expert judgements” OR “assessment*” OR "causality assessment scale*" OR "causality evaluation" OR "diagnosis of ADRs" OR "ADR assessment tool")) AND (“causal” OR “causality” OR “causalities” OR “causally” OR "causation" OR "causative" or EMB.EXACT "pharmacoepidemiology" OR EMB.EXACT "causality" OR MESH EXACT "causality") AND (“drug related side effects” OR “adverse reactions” OR “drug related” OR “side” AND “effects” OR “adverse” AND “reactions” OR “drug related side effects” AND “adverse reactions” OR “drug” AND “related” OR “adverse” AND “reactions” OR “adverse effects” OR “adverse” AND “effects” OR “adverse effects” OR "ADRs" OR "AEs" OR "drug toxic effects" OR "drug surveillance program*") AND ("systematic review" OR "narrative review" OR "scoping review" OR "research synthesis" OR "review" OR "evidence synthesis" OR "gap map" OR "knowledge synthesis" OR "literature map" OR "literature mapping" OR "meta analysis" OR "metaanaly*" OR "metanaly*" OR “comparison” OR “overview”)
Grey literature searches, using relevant keywords, will be conducted using webpages and published documentation of regulatory agencies and relevant societies and organisations such as The Council for International Organizations Of Medical Sciences (CIOMS), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), International Society of Pharmacovigilance ISOP and the European Medicines Agency (EMA), World Health Organization (WHO), International Society of Pharmacovigilance and International Society of Pharmacovigilance (ISOP) and International Society of Pharmacoepidemiology (ISoP).
Data will not be quantitatively analysed. Each causality method will be allocated to one of the three broad categories (expert opinion/global introspection, algorithm or Bayesian/probabilistic) and within each category each method will be assessed by the group, summarised, and its strengths and weaknesses discussed.

Eligibility criteria Causality tools, scales, instruments, and methods used to assess causality at the individual case-level in patients exposed to medicinal products (including vaccines, over the counter medications and herbal or traditional therapies) regardless of age, sex, or pregnancy status in the clinical, industrial or PV centre setting will be included.
Peer reviewed studies conducted within the last 15 years (the beginning of 2008 until the end of 2023) which examine case-level causality assessment methods (including those relevant to a specific system organ class) will be eligible for inclusion. The papers must be review (all types of review e.g., systematic, narrative, literature etc.) articles in the English language which examine causality assessment methodologies at the individual case-level only. The exclusion criteria were selected (too many results would be retrieved otherwise) for feasibility. Additionally, we are only interested in adverse event and adverse drug reaction causality assessment in humans. Methods assessing solely population/aggregate level data will be excluded because our study assesses case-level causality assessment methodologies.
Grey literature will not be restricted on geographical location, but restricted to documents published in English language only.

Source of evidence screening and selection Scientific database search - The first reviewer performed initial searches of Embase and MEDLINE to identify keywords. The keywords will be used to search for relevant review papers which meet the inclusion criteria. A systematic search will be carried out by the first reviewer who will screen the text in the titles and abstracts of the retrieved papers. Any papers where there is doubt regarding their inclusion, will be passed to the second and third reviewers for consensus. Selected papers will then be subject to a full text screen.
Grey literature database search – keywords/terms will be searched in each database and titles and summaries will be screened by the first reviewer. Any documents where there is doubt regarding their inclusion will be passed to the 2nd and 3rd reviewers for consensus. Selected papers will be subject to a full text screen.
The search strategies will utilise an iterative approach. If further search terms are identified in relevant papers during the initial searches, the search strings/keywords will be edited accordingly,

and additional searches will be performed using these terms.

Data management Scientific database search - The first reviewer performed initial searches of Embase and MEDLINE to identify keywords. The keywords will be used to search for relevant review papers which meet the inclusion criteria. A systematic search will be carried out by the first reviewer who will screen the text in the titles and abstracts of the retrieved papers. Any papers where there is doubt regarding their inclusion, will be passed to the second and third reviewers for consensus. Selected papers will then be subject to a full text screen.
Grey literature database search – keywords/terms will be searched in each database and titles and summaries will be screened by the first reviewer. Any documents where there is doubt regrading their inclusion will be passed to the 2nd and 3rd reviewers for consensus. Selected papers will be subject to a full text screen.
The search strategies will utilise an iterative approach. If further search terms are identified in relevant papers during the initial searches, the search strings/keywords will be edited accordingly, and additional searches will be performed using these terms. The three reviewers together will perform a final check of the selected articles, to ensure their suitability and extract relevant data. The data extraction form will be specifically designed to meet the objectives of the review. The data extraction points are listed in other relevant information.

Reporting results / Analysis of the evidence The reviewers will assess the strengths and limitations of each causality assessment method.

Presentation of the results The results of the search and selection of studies will be presented using a PRISMA flow chart. Results will be presented in narrative form and figures and tables will synthesise the data.

Language restriction English language only.

Country(ies) involved United Kingdom, Canada, America, France, The Netherlands, Belgium, Denmark, Italy, Switzerland, Saudi Arabia, Iraq, New Zealand, Japan, Germany, and Norway are represented.

Other relevant information We would like to thank and acknowledge the members of the topic one sub-group for their contributions to idea generation and the document review process.

The author affiliations of Robert Platt are:
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The second affiliation for Dawn Cooper, Miranda Davies and, Saad Shakir is:
The University of Portsmouth School of Pharmacy and Biomedical Science, Portsmouth, UK.
The data extraction points are:
Ref ID
Author(s)
Author affiliation(s) (i.e., health authority, industry, academia)
Year of publication
Country/region of study origin
Type of review (i.e., scoping, systematic, narrative)
Period reviewed (i.e., a paper published in 2021 but reviews literature from 2019-2020)
Specificity by age (neonates, infants, children, adults, elderly, not specified NS)
Specificity by sex (males, females, NS)
Pregnancy status (if applicable – if yes, gestation in weeks)
Specificity by drug, drug class or drug category
Indication(s) for treatment
Concomitant medications? (yes, no, if yes please specify name(s) of drug(s))
How are concomitant medications taken into account during causality assessment?
Specificity by disease(s)
Specificity by type of adverse event or SOC
AE definition specified (yes, no, not sure, not recorded NR)
ADR definition specified (yes, no, not sure, not recorded NR)
Specificity by AE timing (acute events only, chronic events only, acute, or chronic, NR)
Assessment tool methodology (global introspection/expert opinion, algorithm, Bayesian/probabilistic, NS)
Causality criteria (temporality/dechallenge/rechallenge, other please specify)
How many cases was the method tested on?
Where were the cases from? (literature, clinical practice, or pharmacovigilance reports)
How was the tool's inter-rater reliability assessed and what were the findings?
How was the tools validity assessed and what were the findings?
Authors documented limitations of the tool.
Limitation of the tool identified by peers (with citation).
What was the area/speciality or sub-speciality in which the scale was developed?

Keywords Pharmacovigilance; Adverse drug Reaction; International Working Group on New Developments in Pharmacovigilance;; Case-level causality assessment.

Dissemination plans The findings of this scoping review will be published in peer-reviewed journals and presented at conferences.

Contributions of each author

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