ADRχ

October 2023

Background Information

1. Introduction

ADRχ is a new information system designed to support clinicians in assessing adverse drug reactions (ADRs) and adverse drug events (ADEs) as a cause of patient symptoms or adverse test results.

This real-world evidence enables hidden ADR reports to be identified and can help clinicians decide on a course of action. The benefits include:

- Rapid evaluation of potential medicine-related symptoms, test results and challenge options
- Locate potential ADRs quickly across all medicines – FAERS addresses ADRs that are on the datasheet and those that are not
- Identify potential ADRs within medicine class for comparison (e.g. beta blockers)
- Identify potential ADRs within reaction groups (e.g. congenital, familial and genetic disorders)
- Combine patient's drug regimen to assess if symptoms and test results are potentially due to medicine burden
- Improved patient safety and quality of life
- Reduced frequency of consultations

ADRχ utilises ADRs from manufacturers' datasheets (UK/EU/US) presented in an easily accessible, structured format. Uniquely, ADRχ also integrates data from one of the world's largest spontaneous reporting systems, the Food and Drug Administration's Adverse Event Reporting System (FAERS).

FAERS contains over 25 million adverse event reports accumulated since 2004 and from countries all over the world (60% US reports).

ADRχ processes the FAERS data and performs established pharmacovigilance analytics.

Important:

The results from analysing the FAERS data may suggest a low or high association between a medicine and an ADR but causality cannot be inferred from this observational data.

The FDA state the following with regard to the FAERS data;

"***Existence of a report does not establish causation***: *For any given report, there is no certainty that a suspected drug caused the event. While consumers and healthcare professionals are encouraged to report adverse events, the event may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.*

Information in reports has not been verified: *Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.*

Rates of occurrence cannot be established with reports: *The information in these reports cannot be used to estimate the incidence (occurrence rates) of the events reported.*

Patients should talk to their doctor before stopping or changing how they take their medications."

MHRA disclaimer regarding Summaries of Product Characteristics (datasheets)

"I understand that this information is a copy of the Summary of Product Characteristics and patient information leaflet for a medicine, which outline the conditions under which the medicine should be used and information on its known safety.

I understand that this information may be updated several times during the product's lifecycle, and that there could be differences between the information shown here and other information in the public domain.

I understand that the MHRA is unable to offer medical advice and that if a patient has any questions about a medicine they are taking they should contact their doctor or pharmacist. Patients should not stop taking any prescribed medicines without first speaking to a healthcare professional. Suspected adverse reactions to a medicine can be reported to us on a Yellow Card.

I understand that the MHRA has used its best endeavours in publishing this information, but accept that the information may not be the most up to date version for this product."

2. Key points

Clinical Coding

ADRχ uses three main coding systems.

a) **Medical Dictionary for Regulatory Affairs (MedDRA)** – MedDRA is the terminology and hierarchy for reporting adverse events in FAERS. It is also used in UK/EU Summaries of Product Characteristics (datasheets) to state ADRs. MedDRA version 26.0 is used in ADRχ. The terms used in reporting ADRs and in presenting data in FAERS and datasheets need to be standardised. The level of the terms in the MedDRA hierarchy used in ADRχ is the **preferred term (PT)** level.

- Structured MedDRA Queries (SMQs) – *due to the often overlapping or diffuse nature of symptoms and diagnoses, Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc.*[1]

b) **Anatomical Therapeutic Chemical (ATC) classification of medicines**[2] – ATC is the drug classification system overseen by the World Health Organisation. It classifies each medicine according to (example metformin):

- anatomical main group – e.g. alimentary tract and metabolism
- therapeutic subgroup – e.g. drugs used in diabetes
- pharmacological subgroup – e.g. blood glucose-lowering drugs excluding insulins
- chemical subgroup – e.g. biguanides
- chemical substance - the International Non-proprietary Name (INN) is preferred. If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Names)

c) **Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) -** SNOMED CT is a structured clinical vocabulary for use in an electronic health record. It allows for interoperability between systems such as electronic health records and ADRχ[3]

d) **Terminology –** ADRχ use International Naming Nomenclature for medicine names wherever possible. Spelling of all terms is in UK English.

[1] https://admin.meddra.org/sites/default/files/guidance/file/SMQ_intguide_24_0_English.pdf

[2] https://www.who.int/tools/atc-ddd-toolkit/atc-classification#:~:text=Structure,groups%20at%20five%20different%20levels

[3] https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct

Information sources

- **Summaries of product characteristics** – sourced from:
    - Medicines and Healthcare products Regulatory Agency (MHRA) – UK medicine regulator
    - European Medicines Agency (EMA) – European medicines regulator

- **US drug labels**
    - DailyMed – National Library of Medicine

- **Adverse Event Reports** – Food and Drug Administration Adverse Event Reporting System (FAERS). Contains > 25 million voluntary ADR reports from all over the world (60% US) from clinicians, insurance companies, pharmaceutical companies and the public. Reports are added quarterly. The ADRχ data process transforms raw data to ensure quality: deduplication, ingredient name standardisation, adverse reaction term accuracy, statistical processing and quality assurance. The adverse event data has been left in.

- Links to related contents:
    - British National Formulary (BNF) - https://bnf.nice.org.uk/drugs/#a
    - British National Formulary for Children (BNFC) - https://bnfc.nice.org.uk/
    - NHS medicines A-Z website - https://www.nhs.uk/medicines
    - Specialist Pharmacy Service (SMS) - https://www.sps.nhs.uk/medicines/
    - National Institute for Health and Care Excellence (NICE) - https://www.nice.org.uk/

Statistics

ADRχ uses established pharmacovigilance processes to establish disproportionality statistics:

- Case count – this is the number of cases reported into the FAERS system. For ADRχ, only ADRs included are those that have 5 or more reports. For ADRs that appear on the datasheet, the statistics are included irrespective of the number of reports.

- Proportional Reporting Ratio (**PRR**) – the ratio of reports of an ADR for an ingredient to the ratio of the same ADR for all ingredients. A PRR > 1 suggests that the adverse event is more commonly reported for individuals taking the drug of interest, relative to other drugs. So a PRR of 2 indicates that the proportion of adverse reaction reports for the drug-reaction combination (e.g. atenolol-bradycardia) is twice the proportion for all drugs. A PRR < 1 suggests that the adverse event is disproportionately less reported relative to other drugs.

- Reporting Odds Ratio (**ROR**) - the odds of an adverse reaction occurring with a drug compared to the odds of the same adverse reaction occurring with all other drugs in the system.

- PRR and ROR Confidence Interval (**CI**) - the 95% confidence interval is a range of values that are 95% certain to contain the true mean of the population. In ADRχ only results that meet the 95% CI are included.

- Chi-squared (χ^2) – this is a measure of the association between the medicine and the adverse reaction. As with established pharmacovigilance practice, a χ^2 >= 4 is the threshold (except for ADRs included on the datasheets).

3. Background information

We know very little about the overall impact of adverse drug reactions (ADRs) of medicines. Most research that is undertaken focuses on severe ADRs in the hospital setting.

ADRs occurring in the community and with lower severity (in terms of fatality or hospitalisation) are overlooked. This is not surprising as the volume of ADRs, potential and real, is formidable. Moreover, there are no tools that comprehensively support clinical decision-making in this area.

ADRχ is an information system that can be used to identify and guide clinical judgement in the management of potential adverse drug reactions (ADRs), presenting as patient symptoms or test results.

It is designed to be used at the point of consultation or for research. ADRχ presents ADR data from UK/EU Summaries of Product Characteristics and US labels combined with adverse event reports from the Food and Drug Administration's Adverse Event Reporting System (FAERS) data.

By applying established pharmacovigilance statistical analytics, the user is provided with an instant ranking of ADR reports enabling the rapid assessment of the possibility of an ADR causing a patient's symptoms or test results.

A disproportionality analysis methodology is used, which means that users can identify which drugs have a higher or lower proportional reporting ratio for a side effect, relative to all other drugs.

This shows which drugs have an adverse or beneficial, reported, side effect profile and enables comparison with medicines in the same class or with the same indications.

Data Sources

Datasheet side effects and their frequencies

- Summaries of Product Characteristics (SPCs) sources:
    - Medicine and Healthcare products Regulatory Agency (UK);
    - European Medicines Agency (EMA);
- US Drug Labels - DailyMed National Library of Medicine

Spontaneous reports of drug side effects

- Food and Drug Administration (US) - Adverse Event Reporting System (FAERS); voluntary reporting of adverse events by clinicians, legal professionals and consumers
- FAERS contains adverse event reports (60% from the US) from all over the world, including the UK. It is updated quarterly and ADRχ is updated accordingly
- FAERS records contain a range of information including patient age and gender:
    - side-effects experienced (both symptomatic and from test results
    - medicines are taken at the time of the report
    - medicine side-effect status - as assessed by the reporter:
        - Primary Suspect Drug
        - Secondary Suspect Drug
        - Interacting

        - Concomitant
    - indication being treated
    - dose
    - country and date of the report
    - reporter status:
        - Physician
        - Pharmacist
        - Other health-professional
        - Lawyer
        - Consumer
    - outcome:
        - Death
        - Life-Threatening
        - Hospitalization - Initial or Prolonged
        - Disability
        - Congenital Anomaly
        - Required Intervention to Prevent
        - Permanent Impairment/Damage
        - Other
- During the ADRχ production process, the data is analysed to create counts of reported cases which can then be statistically analysed to provide usable information
- Within ADRχ all medicines identified in a reports are included, as the objective is to provide clinicians with supportive information when considering patient safety
- It is important to stress that the results are for reported adverse events. They do not imply causality. However, it is impossible to research all adverse events individually
- Future releases of ADRχ will give users the facility to select filters for results such as age groups and gender.

Coding

- MedDRA - Medical Dictionary for Regulatory Affairs. Codes for adverse drug reactions and indications. Source: ICH; International Council for Harmonisation for Pharmaceuticals for Human Use
- ATC - Anatomical Therapeutic Chemical - codes assigned to medicines according to organ systems and mode of action. Source: WHO; World Health Organisation
- SNOMED CT - Systemised Nomenclature of Medicines - Clinical Terms - international standard clinical healthcare terminology. Source: SNOMED International

Data Analysis

FAERS record processing

- Record deduplication
- Drug name standardisation
- Adverse reaction term standardisation (to MedDRA version 26.0)
- Drug-reaction pair contingency table generation
- Statistics production from contingency tables

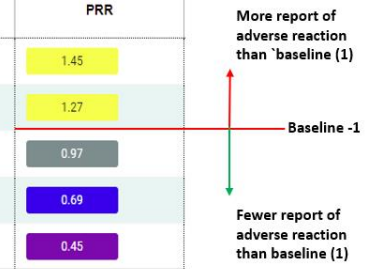
Statistics

- Case count - number of adverse reaction cases reported for each drug
- Total cases - count of ADRs for all drugs
- Expected cases - number of adverse reaction cases expected for each drug
- Proportional Reporting Ratio (PRR) - this is a disproportionality calculation and is the proportion of spontaneous adverse reaction reports for a given drug to the corresponding proportion for all or several other drugs. A PRR greater than 1 suggests that the adverse event is more commonly reported for individuals taking the drug of interest, relative to the comparison drugs. So a PRR of 2 indicates that the proportion of adverse reaction reports for the drug-reaction combination (e.g. atenolol-bradycardia) is twice the proportion for all drugs

Analysis for reaction - nausea

Total cases of nausea reported for all drugs - 1,626,233

Ingredient	Datasheet frequency	Case count	ExpectedCases	PRR
metformin	Very Common	23,069	15,930	1.45
loperamide	Common	3,171	2,504	1.27
methotrexate	Very Common	16,701	17,277	0.97
arsenic trioxide	Very Common	60	87	0.69
haloperidol	Common	821	1,811	0.45



- Reporting Odds Ratio (ROR) - the odds of an adverse reaction occurring with a drug compared to the odds of the same adverse reaction occurring with all other drugs in the system
- PRR and ROR Confidence interval (CI) - the 95% confidence interval is a range of values that you can be 95% certain contains the true mean of the population.

Thresholds

- PRR - most regulatory analysis is set up to identify ADRs that pose a threat to patient safety. Regulators are looking for PRR values that are higher than 1; the higher and the more severe the reaction the more likely they are to take action (e.g. add ADR to the datasheet). ADRχ also includes PRRs lower than 1 to identify those medicines that are 'safer' than others for a given ADR
- Case counts - minimum number of case reports threshold 5 or more
- 95% PRR confidence interval - lower and upper CI range
- Chi-squared statistic - tests for independence and measures the association between the drug being analysed and the adverse reaction. The higher the $\chi 2$ value, the more the observed numbers deviate from expected numbers. The threshold for inclusion in ADRχ is a $\chi 2$ of 4 or more.