Access to Yellow Card Data Guidance Notes

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA), an executive agency of the Department of Health, protects and promotes public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely. The Agency operates post-marketing surveillance systems for reporting, investigating and monitoring adverse reactions to medicines and adverse incidents involving medical devices to safeguard public health.

The safety of medicines is monitored using the Yellow Card Scheme[1] which has been in existence since 1964. The Yellow Card database contains over half a million reports of Adverse Drug Reactions (ADRs) experienced by patients. Each report details an ADR or ADRs that the reporter suspects may be associated with the patient's use of a medicine or drug and the data are coded according to the internationally accepted Medical Dictionary for Regulatory Activities (MedDRA)[2]. The Yellow Card Scheme is voluntary for healthcare professionals and members of the public, there are however, specific reporting requirements for the pharmaceutical industry.

The 2004 Independent Review of Access to the Yellow Card Scheme[3] recognised the research potential of the Yellow Card database, as one of the largest single compendiums of suspected adverse drug reactions in Europe. Following the Review the systems described in this guidance document have been developed to ensure that (any) information included in the database that is subject to release on request under the Freedom of Information Act[4] (FOIA) will be readily available while at the same time protecting the confidentiality of individuals and their personal data as the Data Protection Act[5] (DPA) requires.

2. GENERAL PRINCIPLES

The MHRA welcomes the interest that other organisations and individuals have expressed in researching the Yellow Card database in the interests of patients and for public health benefit. The Agency is conscious of the duty of confidentiality to patients and reporters that is required by the DPA. Research on confidential data is nevertheless lawful when it is undertaken with the consent of the subjects involved and in accordance with ethical and scientific principles.

The MHRA's purpose in opening the database is to maximise the accumulated value of the database for the benefit of patients and public health. This guidance summarises the arrangements the Agency has set up to enable any organisation or individual/applicant to access the Yellow Card database in order to carry out independent research or investigations. Any UK or non-UK resident, may apply for access to Yellow Card data and there are no restrictions in respect of the scientific experience or qualifications of any applicant. If you require any assistance completing the application form or are unsure which parts to fill in, please contact the MHRA.

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[1] Further information about the Yellow Card Scheme can be found on the MHRA website at www.yellowcard.mhra.gov.uk
[2] http://www.meddramsso.com/
[3] Report of an Independent Review of Access to the Yellow Card Scheme, TSO, London 2004
[4] http://www.hmso.gov.uk/acts/acts2000/20000036.htm
[5] http://www.legislation.gov.uk/ukpga/2018/12/contents/enacted

However, in providing access the MHRA needs to be assured of the appropriateness and quality of the research and the scientific integrity of proposals. Applicants are therefore required to accept the following principles:

1. The proposal must be of potential scientific value and/or have significant public health implications. The research methods must be described in the proposal so that their scientific merit and feasibility can be independently reviewed and evaluated.

2. Any potential benefits and risks for patients during the course of the research process and/or anticipated as a consequence of the research should be set out in the proposal.

3. Data from the Yellow Card Scheme that is subject to the Data Protection Act, such as individual personal data, must not be provided to third parties without the approval of the Pharmacovigilance Expert Advisory Group (PEAG) and the consent of the reporter and patient.

4. The research must be conducted only by the principal applicant and co-applicants named in the application.

5. Any change or amendment to the research plan or methodology must be notified in writing to the MHRA for approval and should the principal applicant and/or co-applicants change during the course of the study the MHRA must be notified.

6. Any information which identifies a patient and/or reporter that is made available to a principal applicant will be released on a confidential basis. The applicant must ensure appropriate safeguards are in place to restrict further access only to those named in the research application.

7. Applicants are obliged to follow the general principles of the Human Rights Act 1998[6], the Data Protection Act 1998[7] and the principles set out for research by the Department of Health[8].

2.1. Limitations of Yellow Card data

It is important to note that causality is not proven for these Yellow Card reports. Reporters are encouraged to report spontaneous 'suspected' Adverse Drug Reactions (ADRs) but the reporter does not have to be sure that the drug caused the reaction – a mere suspicion will suffice. These reports may be an adverse reaction to the use of a particular drug or they may be due to coincidental illness that would have happened in the absence of treatment. The limitations of a spontaneous reporting scheme such as the Yellow Card scheme include an unknown level of underreporting. ADR reporting rates may be influenced by seriousness of reaction, their ease of recognition and publicity about a drug. Yellow Card data cannot be used to determine incidence of a particular ADR as denominator data is not available.

2.2. Confidentiality of Yellow Cards

Since September 2000 all patient identifiers have been removed from the Yellow Card in line with the Data Protection Act (DPA) 2018 and the General Medical Council (GMC) guidelines on

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6 http://www.hmso.gov.uk/acts/acts1998/19980042.htm

7 http://www.hmso.gov.uk/acts/acts1998/19980029.htm

8http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/ResearchGovernanceArticle/fs/en?CONTENT_ID=4002130&chk=pebh9u

confidentiality (General Medical Council, 2000)[9]. Prior to this date, to identify duplicate reports reporters were asked to enter the patient's name and date of birth on the Yellow Card. The inclusion of identifying details also facilitated the follow-up of reports when additional data were requested.

In accordance with the legal requirements of the DPA, the MHRA has subsequently updated the Yellow Card database to remove all patient identifiers; and the MHRA will not release any information that could identify the person who submitted a Yellow Card, (the reporter), or the patient without the consent of the person(s) concerned.

2.3. Responsibilities of applicants provided with Yellow Card data

The principal applicant has responsibility for ensuring that any research using Yellow Card data has been clearly defined within their application and that these comply with the general principles as defined in this guidance document (listed above) and the undertakings provided on the application form. The principal applicant must ensure that the data are held securely and used solely for the defined intended purpose.

As with all other information held by the MHRA, release of Yellow Card data is subject to the Data Protection Act (DPA). Some information is already routinely published or provided on request. Applicants should therefore consult the MHRA website[10] before developing details of the proposal and deciding on the range of data to be requested.

2.4. Data Protection Act (DPA)

The DPA[11] is primarily concerned with requests from individuals to know what personal information about them is held by, in this case, the MHRA (this is known as a subject access request). The DPA applies to data from which it is possible to identify a living individual. Subject to certain exemptions, it prohibits disclosure, without consent, of any personal information that identifies a living person. In certain cases this may apply to release of specific non-personal ADR data from a Yellow Card that may indirectly identify a reporter or a patient or in cases where only a limited number of cases exist.

2.5. Categories of Yellow Card data

Category Ia Data

Anonymised aggregated adverse drug reaction (ADR) data that do not identify the patient or reporter are known as Category Ia data, and are proactively provided on the MHRA website in the format of interactive Drug Analysis Prints (iDAPs) which are regularly updated[12]. Guidance on their interpretation is also available on the same website. Requests for these data are freely available under FOIA and are included in the Agency's FOIA Publication Scheme. Therefore, all anonymised Category Ia data will be available from the MHRA upon request on the same basis as other FOI requests that the Agency receives[13].

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[9] The GMC Guidelines were updated in April 2004 'Confidentiality: Protecting and Providing Information'. http//www.gmc-uk.org/standards/secret.htm

[10] Go https://yellowcard.mhra.gov.uk/idap

[11] https://www.gov.uk/data-protection

[12] Go to https://yellowcard.mhra.gov.uk/idap

[13] Go to https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

Category Ib Data

There are further data that can be provided from individual Yellow Cards that exclude any information that identifies a reporter and/or patient or provides any opportunity for the recipient to contact or identify the reporter and/or patient. Release of these data, known as Category Ib data, may include the age categories of the patients; the proportion of males and/or females who experienced the reaction; the drug or drugs involved; the dose and duration of drug therapy; the route of drug administration and the suspected adverse drug reaction(s) that the patient experienced (a full list of these Category Ib fields is provided at Annex D). These data are generally releasable under the FOIA, without consideration by PEAG, although provision of these data will depend on the number of cases held by the Agency. In this context, among other Government departments, the Office of National Statistics (ONS) will only release information when at least five cases are included in any data subsets[14]. PEAG has adopted the same policy to prevent identification of patients and/or reporters. Requests for data that have less than five cases in any one cell, will be aggregated prior to release. Any aggregation will be clearly marked when the data are provided. The MHRA will not charge for release of Category Ib data unless the time taken to edit or redact the data requested exceeds 24 working hours.

Category II Data

Certain data contained on the MHRA database may indirectly identify either the reporter or the patient. These data fields may, for example, include patient unique details in the narrative text provided by the reporter, the patient's medical history, dates of drug administration and reaction and specific test results relevant to the suspected adverse reaction, which might enable the patient to be identified. Requests for reporter and patient details or for data that may identify the reporter or patient are considered as Category II data.

All Category II data requests will be reviewed by PEAG. In certain cases ethical approval may also be required. Requests for data that relate to a small number of ADR cases may also identify the reporter or patient and these requests will have to be considered by the Group. In addition, any requests for actual images of Yellow Cards or for large subsets of these data would be referred to PEAG.

The Independent Review proposed arrangements that would satisfy legal and ethical requirements for studies that might be undertaken that would involve direct access to confidential personal data on patients and/or might also involve direct access by the researcher to patients. A number of safeguards have been established to ensure that release of these data would follow scientific and ethical approval and that reporter and patient consent would be obtained prior to release of any of their identifiable data. These include requests in which the reporter would need to be approached in the first instance so that the reporter could decide whether the patient should be asked for his/her consent. This would be necessary for a genetic research study to investigate whether certain patients are predisposed to specific ADR(s) or when a researcher requested access to the entire database to develop signal detection methodologies. Under such circumstances, these applications will require ethical approval from a Research Ethics Committee (REC) through the Central Office for Research Ethics Committees (COREC[15]) system.

[14] The ONS is in the process of a disclosure review of health statistics. When this is finalised PEAG may follow a similar approach to release of subsets of data.
[15] http://www.corec.org.uk/

Following both scientific and ethical approval the MHRA will be responsible for contacting the reporter to ask if he/she is prepared to assist the applicant with the study. That responsibility will not be delegated outside the Agency under any circumstances. If appropriate, the reporter should also be told to ask the patient if they are willing to be contacted by a researcher in the context of a particular study. Consent from both the reporter and the patient must be obtained before their contact details are disclosed to the researcher. The MHRA will require a short summary of the research proposal in layman's terms for the reporters to give to patients when informing them of the proposed research and possible implications.

It will be the responsibility of the reporter to decide in each case whether a patient should be asked to participate. The MHRA will allow a time period of two months for the reporter to respond before sending a reminder letter to the reporter. If no response is received within a month of sending the reminder the Agency will not pursue the request further. In writing to the reporter the MHRA will endorse participation for those studies approved by the Committee and REC but will not further influence their decisions. Once responses are available from reporters the MHRA will inform the researcher of the proportion of patients who have agreed to assist.

2.6. Data of deceased patient and reporters

As a general policy[16] the ONS treats the deceased the same as the living as they consider that there remains a duty of confidence owed to the deceased, even though the DPA refers to living individuals and does not extend to the deceased. PEAG supports this view and for this reason, all requests for release of data from deceased patients will be considered under the same conditions as the living. If a patient has deceased the reporter as a matter of courtesy should consider whether to contact the next of kin if he intends to disclose details of the patient for research.

When a reporter who has submitted a Yellow Card has died the decision on whether to contact the patient for consent would be referred by the MHRA to the reporter's NHS (or private) successor in-post.

2.7. Finance

The Agency will then charge a fee based on time to prepare the data. This will be calculated on the hours of work and the number of Agency personnel required and will be detailed in the contract. This will enable requests for case details to be provided to be the most economical to the applicant, while the costs for research which requires the Agency to contact the reporter and through them the patient will be proportionate to the amount of work required. In the latter case, additional costs including payment of reporters and patients for their time and inconvenience will have to be borne by the applicant. All fees are non-refundable to applicants even if the response from reporters (and patients) is poor.

2.8. Additional fees for pre-1991 data

[16] The ONS is also reviewing its policy in relation to the deceased.

Yellow Card data is held on database known as Sentinel, prior to 1991 data was held in the Norsk database, the original computer system on which the Product Licence Database was stored. When Norsk data were transposed onto the database only basic details from each ADR report were added to the new database, such as, the name of the drug, the reaction and the outcome of the reaction. For applicants who request pre-1991 Yellow Card data an additional charge may be incurred for the time required for Agency staff to retrieve additional data from old ADR case reports not currently held on the database if more than the basic details are required the level of which will be discussed with the Agency.

3. APPLICATION FORM COMPLETION NOTES

When applying for access to Yellow Card data (Category II[17]) all applicants must complete the application form at Annex A and confirm that they have read and accept the undertakings on the application form and these guidance notes. The undertakings require that applicants do not disclose the data to persons not named on the application form or use the data for purposes not described in the research proposal. All data released by the MHRA for research is subject to the condition that the principal applicant must inform the MHRA of any issues effecting the safety of a medicine, whether licensed or unlicensed, that are identified during the research and submit all resulting publications to the Agency at least four calendar weeks prior to submission (see Section I).

The details of the proposed use of the data and any statistical analysis should be provided in the protocol which should append to the application form. If approval has been given by a NHS research ethics committee prior to the application this should be mentioned and the ethics committee and its reference number specified[18]. Applicants should be aware that prior approval by an ethics committee does not predetermine approval by PEAG. All relevant agreements with other academic, commercial or other organisations should be disclosed. If it is anticipated that the research may have a patentable or commercially exploitable outcome this should also be recorded as the MHRA reserves the right to a share in any commercially exploitable outcome.

All applications should preferably be emailed directly to the MHRA at the following address type2yellowcarddata@mhra.gov.uk or can be posted to the address provided below.

3.1. Guidance for completing the application form

Section A - PERSONAL DETAILS

The principal applicant and all co-applicants should provide their contact details within this section.

Section B - TITLE AND SUMMARY OF THE PROPOSAL

The applicant should set out the title of the proposal, the name and address of the Department / Institution / place at which the research will be conducted and the proposed start date.

In addition applicants should provide a short summary of their proposal including the key goals and set out the relevance of the research to future patient care and/or public health.

[17] Definitions of data categories are provided in section 3.1
[18] In most cases it is unlikely that ethical approval will have been obtained prior to scientific scrutiny by PEAG.

Section C – USE OF OTHER DATABASES

The combination of Yellow Card data with other databases may have the potential to identify patients and/or reporters. All applicants must state whether they intend to use the Yellow Card data in combination with another database or any other data sources.

Section D - DETAILS OF PROPOSAL

Applicants should clearly state if contact is required with the Yellow Card reporters. Also all the data fields which are required for the study should be selected at this stage.

Section E - RELEVANT APPLICATIONS AND PUBLICATIONS

Applicants should include details of all their previous or ongoing research that utilised Yellow Card data.

Section F - SECURITY & CONFIDENTIALITY

PEAG and the MHRA consider that confidentiality of Yellow Card data is paramount. For this reason any release of data that is subject to the DPA must be subject to stringent conditions.

Applicants must confirm that they will guarantee the ongoing confidentiality of the data by abiding by the principles in the DPA (Annex B) and specify where any data released to them for research will be held and what security measures will be in place to prevent disclosure to third parties.

Section G - PUBLICATION

The MHRA encourages publication of research using the Yellow Card database. However, applicants must state on the application if they intend to publish or place the results of the research in the public domain.

The Agency requires that all publications or other data based on research using Yellow Card data are submitted at least four calendar weeks in advance of any public release of research findings. This requirement is not to impose a delay on publication but is necessary to enable the MHRA to fulfil its statutory responsibilities and arrange any necessary regulatory action required in the light of the research findings. Any regulatory action would be timed to coincide with publication. The Agency may also offer comments on the proposed publication but the principal applicant will not be obliged to accept these. However, in situations in which the MHRA has concerns about the implications of the research and the applicant does not acknowledge these the Agency reserves the right to comment independently.

A separate pre-publication notification must be submitted to the PEAG for every publication based on released Yellow Card data.

Section H - RELEVANT RESEARCH HISTORY

All applicants (the principal and all co-applicants) should include a list of their relevant research history and a brief summary with each application. A summary of relevant experience and/or

publications which are of particular relevance to the current application should be highlighted. Please note no more than ten relevant publications should be provided.

Section I - SUPPLEMENTARY INFORMATION

For audit purposes, applicants are requested to provide details of the source from which they learnt about this application process for access to the Yellow Card database.

Section J – UNDERTAKINGS BY APPLICANT(S)

The principal applicant and all co-applicants must sign and date the form to agree to all the terms and conditions set out by the MHRA

PROTOCOL CHECKLIST

Applicants must ensure that the protocol which they should append to the application form covers all the points listed in the checklist, including any specific limitations of the study. If it is felt that any of these points are not relevant for the planned study, then it is important that the reason for omission is stated.

Patient and user group involvement

Some studies using Yellow Card data may benefit from the involvement of patient or user groups in the planning and refinement stages, and/or in the interpretations of results, in the dissemination and in informing plans for further work. Please indicate whether patients/users groups will be engaged in any of the aforementioned ways.

4. REVIEW PROCESS

Upon receipt of an application a validation check will be made. If further information is required before the application can be processed, the principal applicant will be contacted before the application is accepted. Once an application has been logged the principal applicant will receive an acknowledgement for the application in the form of a letter or e-mail depending on the mode of submission. A reference number for the application will then be provided along with the intended date of review by PEAG.

4.1. Outcome of the review process

The principal applicant will be informed of the outcome of their application following review by PEAG. Where the application has been approved by the Expert Advisory Group, the principal applicant will receive the requested data from MHRA staff within a defined timeframe. If an application is refused the applicant will be informed of the reasons and have an opportunity to appeal (section 4.3) or re-submit an amended application to the Committee.

4.2. Appeal mechanism

If the MHRA accepts the advice of PEAG to turn down an application for data, the unsuccessful applicant will be sent a letter setting out the reasons why. The applicant will be told that he/she has 28 days from the date of the letter to make representations, and that these should be made in writing to the Yellow Card PEAG Secretary as appropriate. The applicant will be informed that once this 28 day period has expired, he/she will have to make a fresh application.

If an appeal is to be carried out then the Licensing Authority will appoint a person or persons to undertake a review of the documentation. A letter will be sent to the applicant with the outcome of the appeal. The decision of the Licensing Authority will be final.

5. CONTACT FOR FURTHER INFORMATION

For further information, please send an email directly to: type2yellowcarddata@mhra.gov.uk.

Or you can make contact via the following address or telephone number:
Medicines & Healthcare products Regulatory Agency
10 South Colonnade
Canary Wharf
London
E14 4PU
Tel: 020 3080 6000 (Central Enquiry Point)

Glossary

Adverse Drug Reaction (ADR)
An adverse reaction is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from use of a medicinal product within the terms of the authorisation, as well as outside of the terms of the marketing authorisation including overdose, misuse, abuse and medication error and occupational exposure.

Co-applicant
A co-applicant is a researcher who will have significant intellectual input into, and part responsibility for, the research if the application is successful.

Committee on Safety of Medicines (CSM)
The CSM was one of the independent advisory committees established under the Medicines Act (Section 4) which advises the UK Licensing Authority on the quality, efficacy and safety of medicines in order to ensure that appropriate public health standards are met and maintained. In November 2005 the CSM was replaced by the new Commission on Human Medicines (CHM).

Medical Dictionary for Regulatory Activities (MedDRA)
The internationally accepted medical terminology for use in drug regulation. Developed under the auspices of the ICH and based on MEDDRA (Medical Dictionary for Drug Regulatory Affairs) which was in turn based on the MHRA's medical dictionary.

Medicines Act
The Medicines Act was given Royal Assent in October 1968. It provided for a comprehensive system of licensing affecting manufacture, sale, supply and importation of medicinal products into the UK. Medicines regulation in the UK is now governed by a combination of powers under the Act on EU law.

Medicines and Healthcare products Regulatory Agency (MHRA)
On 1 April 2003, the Medicines and Healthcare products Regulatory Agency (MHRA) replaced the Medical Devices Agency (MDA) and the Medicines Control Agency (MCA). The MHRA is an Executive Agency of the Department of Health with Trading Fund status. The MHRA is committed to safeguarding public health by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

Norsk Database
The original computer system on which the Product Licence Database was stored.

Pharmacovigilance
Pharmacovigilance is the process of (a) monitoring medicines as used in everyday practice to identify previously unrecognised or changes in the patterns of their adverse effects; (b) assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; (c) providing information to users to optimise safe and effective use of medicines; (d) monitoring the impact of any action taken.

Principal applicant
A principal applicant is the lead researcher who has the main intellectual input into, and responsibility for the research if the application is successful. This is the individual with whom the MHRA will correspond about the application.

Public domain
Information that is openly available to everyone and not subject to copyright protection.

Redaction
The careful editing of a document to remove confidential information.

Reporter
Reporters of adverse drug reactions via the Yellow Card Scheme are health care professionals (e.g. doctors, dentists, coroners, pharmacists, nurses, radiographers and optometrists etc). The

Yellow Card Scheme is voluntary for members of the public and health care professionals, they also report indirectly to us via the pharmaceutical industry.

Side effect
A consequence other than the one for which an agent or measure is used.

Signal detection
A signal can be defined as reported information on a possible causal relation between an adverse event and a medicine, the relation being previously unknown or poorly documented. The Yellow Card Scheme can be used to detect signals that require further Pharmacovigilance investigation.

Trading Fund
A Trading Fund is a financing framework for Government operations, covering operating costs and receipts, capital expenditure, borrowing and net cash flow, which gives an agency greater freedom to manage its financial affairs than if its costs are met by its parent Department.

UK Licensing Authority
UK Government Ministers of Health and Agriculture.

List of abbreviations

ADR	Adverse drug reaction
COREC	Central Office for Research Ethics Committees
CSM	Committee on Safety of Medicines
DAP	Drug Analysis Print
DPA	Data Protection Act 2018
FOIA	Freedom of Information Act 2000
GMC	General Medical Council
REC	Research Ethics Committee
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
ONS	Office of National Statistics
PEAG	Pharmacovigillance Expert Advisory Group

Annex B

The Data Protection Act 1998 Principles (Schedule 1)[19]

1. Personal data shall be processed fairly and lawfully and be transparent, in particular, the processing of personal data is lawful only if and to the extent that (a)at least one of the conditions in Schedule 9 is met, and (b)in the case of sensitive processing, at least one of the conditions in Schedule 10 is also met.
2. The purpose for which personal data is collected on any occasion must be specified, explicit and legitimate, and personal data so collected must not be processed in a manner that is incompatible with the purpose for which it is collected.
3. Personal data must be adequate, relevant and not excessive in relation to the purpose for which it is processed.
4. Personal data undergoing processing must be accurate and, where necessary, kept up to date.
5. Personal data must be kept for no longer than is necessary for the purpose for which it is processed.
6. pPrsonal data must be processed in a manner that includes taking appropriate security measures as regards risks that arise from processing personal data.

[19] http://www.legislation.gov.uk/ukpga/2018/12/part/4/chapter/2/crossheading/the-data-protection-principles/enacted

Annex C

Category I releasable data fields (Category Ib data)

Category I data case details listed below are releasable under the Freedom of Information Act (FOIA) without consideration by the PEAG. These are known as Category Ib data. Provision of these data will depend on the number of cases held by the Agency. The MHRA will not release any data subset in which there are five or fewer cases per cell. This is necessary to prevent identification of patients and/or reporters. Where there are less than five cases per cell the data will be aggregated with adjacent cells. Any aggregation will be clearly marked on the dataset.

Patient age categories (<18, 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, >85 years)
Patient sex (number of female and male patients)
Suspect drug(s)
Dose of suspect drug
Route of administration
Duration of treatment
Suspected adverse drug reaction(s)
Adverse drug reaction outcome(s)
Time to onset
Past medical history
Year of receipt