SCOPE Work Package 4
ADR Collection

Tools for Measuring and Improving the Quality of Reports in National Adverse Drug Reactions Databases

SCOPE

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Contents

Acknowledgments

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide an overview of tools for measuring and improving the quality of reports in national adverse drug reactions (ADR) databases and to encourage European Union (EU) Member States (MSs) to use these tools in their databases. Continuously monitoring and improving the quality of reports ensures that better quality data enters the next step of the pharmacovigilance (PV) process, i.e. signal detection.

MSs may wish to develop their own procedure for the quality assurance of data in their database to be able to have a comprehensive tool adapted to the specificities of both their own procedure of processing ADR reports and their own ADR database. In this document, a case study on the Medicines and Healthcare products Regulatory Agency (MHRA) procedure for monitoring and reporting on ADR data quality in their PV database is presented as an example of a quality assurance procedure. In addition, as a tool to support defining an internal procedure for quality review of ADR data in a PV database, a checklist was developed and is also presented in this document. MSs can use this checklist along with the MHRA case study to guide the development of the procedure that best fits their national needs.

Other tools presented in this document include the EudraVigilance (EV) Feedback Report, the vigiGrade completeness score and the Clinical Documentation tool (ClinDoc). These tools can be used to complement internal procedures for quality assurance. The EudraVigilance (EV) Feedback Report, developed by the European Medicines Agency (EMA), is used by EU MSs, while the vigiGrade completeness score, developed by Uppsala Monitoring Centre (UMC), is used by countries participating in the World Health Organisation (WHO) Programme for International Drug Monitoring. A brief overview of the former UMC tool, called Documentation grading – completeness score, is also included within this document for information purposes. Finally, the ClinDoc is a novel tool focused on the quality of clinical data within an ADR report and was developed by the Netherlands Pharmacovigilance Centre Lareb as part of the Web-Recognising Adverse Drug Reactions (WEB-RADR) Project. The ClinDoc is presented in this document as a case study.

1.2 Background

The Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action has been created to support operations of pharmacovigilance (PV) in the EU following the requirements introduced by the 2010 European PV legislation[1,2,3], which came into force in June 2012. Information and expertise on how regulators in MSs run their national PV systems was gained in order to develop and deliver guidance and training in key aspects of PV, with tools, templates and recommendations. The aim of the SCOPE Joint Action was to support consistent approach across the EU network for all PV operations, in order to benefit medicines safety monitoring and communications to safeguard public health.

SCOPE was divided into eight separate Work Packages (WP), with five WPs focusing on PV topics to deliver specific and measureable objectives, ranging from improvements in adverse drug reaction (ADR) reporting to assessment of quality management systems.

WP4 ADR Collection focused on national schemes for the spontaneous reporting of ADRs and was aimed to provide National Competent Authorities (NCAs) with a full understanding of and good practices within national systems for collecting ADRs. Information was gathered from European MS institutions to understand their national ADR system, PV IT system capabilities, as well as implementation of patient reporting, types of reporting forms developed, and electronic reporting developments, including those from clinical healthcare systems[4]. This information was used to create best practice guidelines, performance indicators and a media toolkit for raising awareness of ADR reporting systems which will be supported through delivery of a training course for institutions.

1.3 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
ClinDoc	Clinical Documentation Tool
CHAFEA	Consumers, Health and Food Executive Agency
CIOMS	Council for International Organisations of Medical Sciences
DKMA	Danish Medicines Agency
EEA	European Economic Area
EMA	European Medicines Agency

[1] Directive 2010/84/EU of the European Parliament and of the Council

[2] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[3] Commission Implementing Regulation (EU) No 520/2012

[4] SCOPE WP4 – ADR Collection Topic 1, 1a, 2, 5 Survey Report. Available from URL: http://www.scopejointaction.eu/_assets/files/SCOPE-WP4-Topic-1,2,5-survey-report.pdf [Accessed 24 March 2016]

Terminology	Description
EU	European Union
EV	EudraVigilance
EVDAS	EudraVigilance Data Analysis System
FDA	Food and Drug Administration
GP	General Practitioner
GVP	Guideline on Good Pharmacovigilance Practices
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State(s)
MTS:PTC	MedDRA Term Selection: Points To Consider
NCA	National Competent Authority
PV	Pharmacovigilance
PT	Preferred Term
SAS	Statistical Analysis Software
SCOPE	Strengthening Collaboration for Operating Pharmacovigilance in Europe
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
UMC	Uppsala Monitoring Centre
QA	Quality Assurance
WEB-RADR	Recognising Adverse Drug Reactions
WI	Work Instructions
WHO	World Health Organisation
WP	Work Package
YCC	Yellow Card Centre
YCS	Yellow Card Scheme

2. SCOPE survey results

Spontaneous ADR reporting is an important source of safety information about medicines, especially for signal detection and identification of rare and very rare ADRs. At the level of the EU, legal requirements regarding the collection, data management and reporting of suspected ADRs are in place[5,6,7]. Guideline on Good Pharmacovigilance Practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, addresses these legal requirements applicable to NCAs in MSs, Marketing Authorisation Holders (MAHs) and the European Medicines Agency (EMA)[8]. Complementary to GVP Module VI, several other guidelines and guidance documents relating to the quality of ADR data are currently being used, including the International Conference on Harmonisation (ICH) E2B Guideline[9], the Medical Dictionary for Regulatory Activities (MedDRA) Term Selection: Points To Consider (MTS: PTC)[10], the EudraVigilance (EV) guidance documents and VigiFlow User Guide[11]. In addition to these, to support MAHs, some NCAs, such as the Medicines and Healthcare products Regulatory Agency (MHRA) and Danish Health and Medicines Authority (DKMA) have developed national guidance documents for industry on best practices in reporting Individual Case Safety Reports (ICSRs)[12,13].

Continuously monitoring and improving the quality of data in national ADR databases is a necessity, since only reports of good quality can produce reliable signals. In Audit of National Reporting Systems of the SCOPE Joint Action WP4, the information about EU MS practices with regard to the use of indicators and metrics for assessing the quality of reports was collected through a questionnaire completed by EU MSs. The MSs were asked if they use any indicators or metrics for assessing the quality of the reports and, if so, to specify what indicators or metrics they use.

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[5] Directive 2010/84/EU of the European Parliament and of the Council

[6] Regulation (EU) No 1235/2010 of the European Parliament and of the Council

[7] Commission Implementing Regulation (EU) No 520/2012

[8] Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1), EMA, 8 September 2014. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf [Accessed 24 March 2016]

[9] ICH E2B Guideline: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports Available from URL: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html [Accessed 24 March 2016]

[10] MedDRA Term Selection: Points to Consider. Available from URL: http://www.meddra.org/how-to-use/support-documentation [Accessed 24 March 2016]

[11] VigiFlow User Guide for version 5.2. Available only to countries participating in WHO Programme for International Drug Monitoring from https://adr.who-umc.org/login.asp [Accessed 24 March 2016]

[12] Best Practice In Reporting Of Individual Case Safety Reports (ICSRs), Version 1.0, MHRA, February 2011.

[13] Guide To Individual Case Safety Reporting: Guide to industry, Version 1.0, DKMA, June 2015. Available from URL: https://sundhedsstyrelsen.dk/en/Feeds/~/media/B95846036A24403695DD5C30DD105D91.ashx [Accessed 24 March 2016]

Twenty-seven MSs provided answers to the question about their usage of indicators and metrics for assessing the quality of the reports: 13 MSs reported that they do use indicators or metrics for assessing the quality of reports, while 14 MSs reported not using them. All 13 MSs that reported using indicators or metrics provided further information on what indicators or metrics they use. All 13 MSs provided information about using the Uppsala Monitoring Centre (UMC) completeness score: 8 MSs did use the UMC completeness score, while 5 MSs did not use this indicator. 12 MSs provided information about using the EV feedback report: 10 MSs did use the EV feedback report, while 2 MSs did not use this indicator. In total, 6 MSs used both the UMC completeness score and the EV feedback report as tools for assessing the quality of reports. Additionally, 5 MSs reported that they use other indicators or metrics, while 7 MSs did not use additional tools. Additional tools used by the MSs who provided an answer to this question included internally developed indicators that are included in Standard Operating Procedures (SOPs) and regular compliance checks or quality audits. **Figure 1** shows what indicators or metrics are used for assessing the quality of reports by EU MSs.

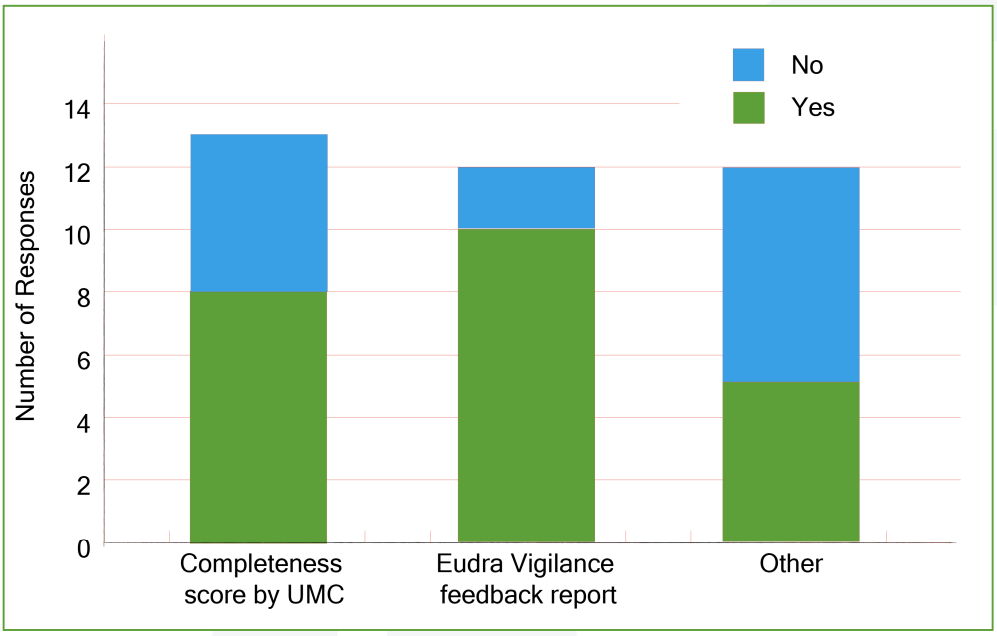

Figure 1 Indicators or metrics used by EU MSs for assessing the quality of reports in national ADR databases

In addition, for the purpose of complementing the results of the SCOPE WP4 survey, a supplementary search of VigiBase was performed by UMC on the request of SCOPE WP4 for EU/ European Economic Area (EEA) countries for the period 2009-2013. In general, the results of this tailored UMC search of VigiBase showed that, although the completeness score varies between countries and also varies over time within countries, the average completeness score for the EU/EEA is stable over time and can be considered satisfactory. It should be noted that completeness scores are not a direct indicator of the quality of data processing, because the score also depends on the amount of data contained in the ADR reports submitted to the NCA. Therefore, MSs cannot be directly compared without taking into account the complexity of factors relating to their national reporting systems and also to national ADR databases, since these have an impact on the completeness score. For example, some MSs do not submit complete ICSRs to VigiBase, which means that completeness score for their reports in VigiBase is lower than it would be if complete reports were submitted. It should also be taken into account that completeness scores are calculated based on the dates when the reports were last updated in VigiBase, which means that the frequency of submitting the reports to VigiBase may also influence the score. The results of UMC search of VigiBase tailored for SCOPE WP4 are presented in **Figure 2** and **Figure 3**.

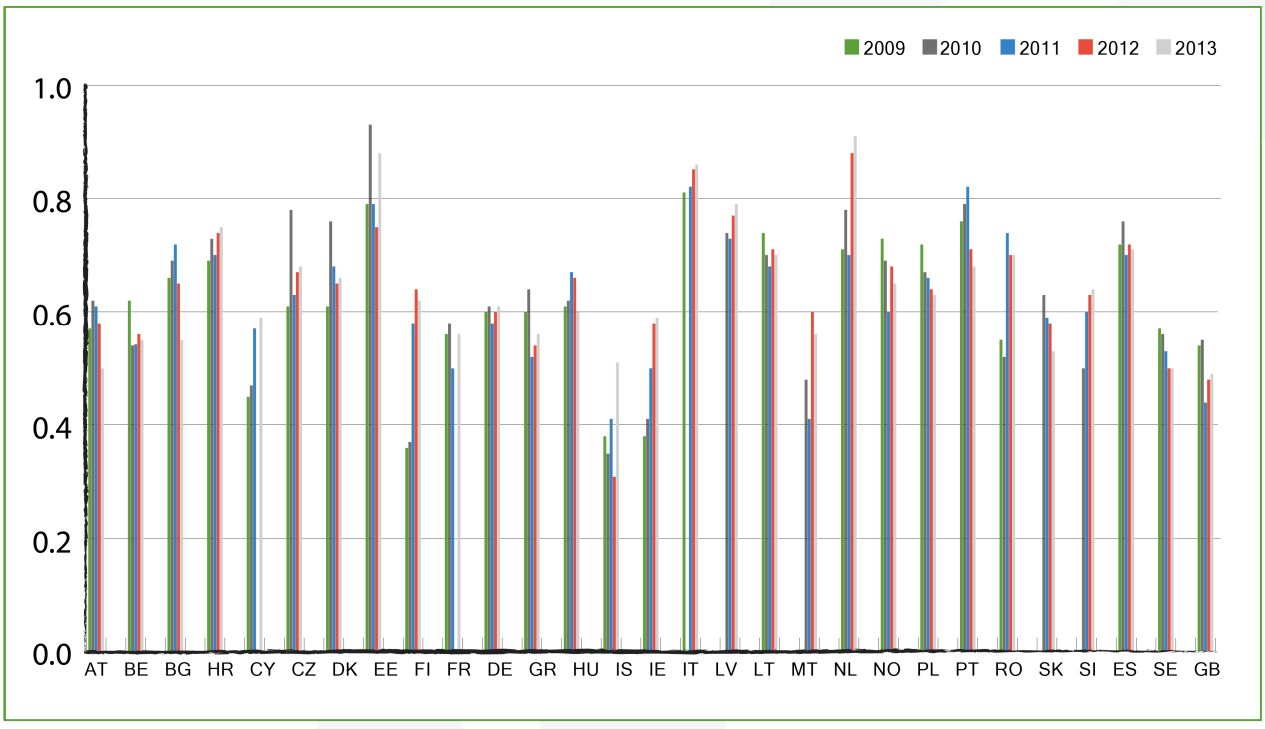

Figure 2 Yearly completeness scores for EU/EEA countries

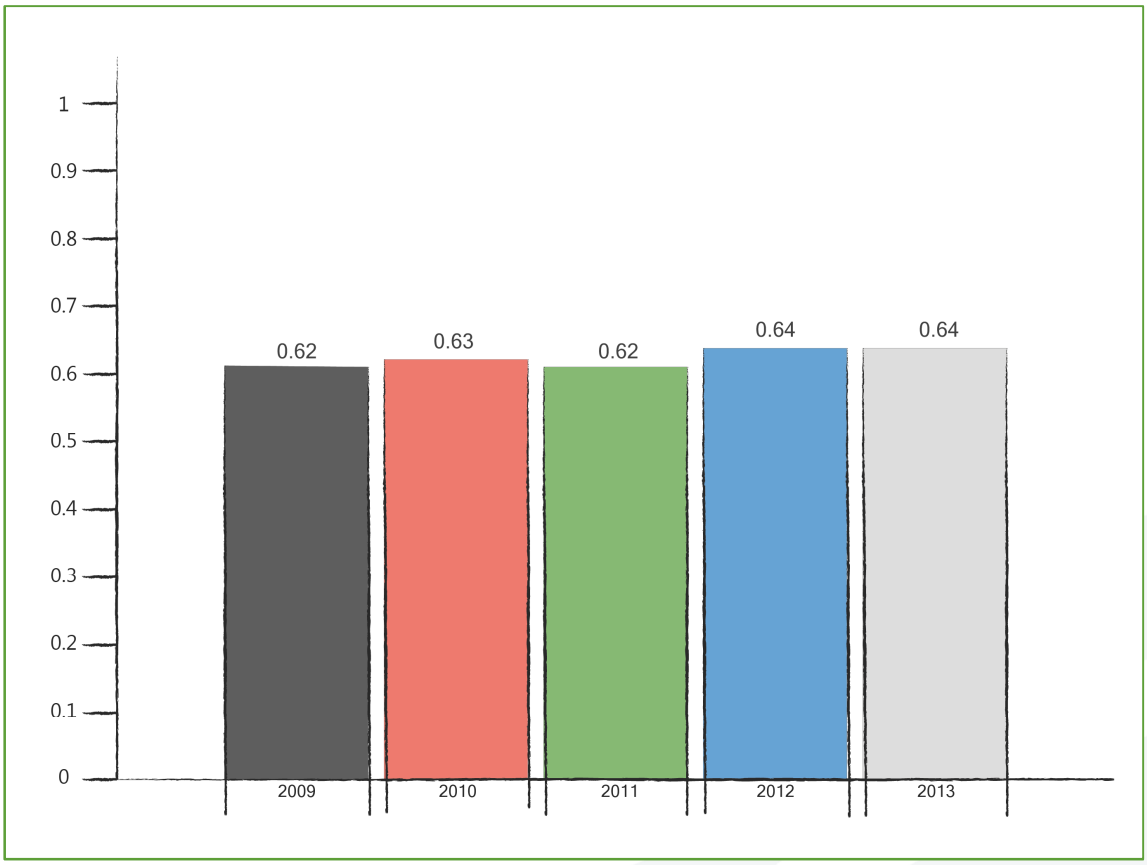

Figure 3 Average completeness score for EU/EEA

3. Procedure for monitoring and improving the quality of reports in National ADR databases

A comprehensive tool, such as an internal procedure for quality assurance of ADR data, is essential for MSs to ensure a good quality of ADR reports in their PV databases. In this section, the case study of the MHRA procedure for monitoring and reporting on ADR data quality in their PV database is presented. A checklist for defining the internal procedure for quality review of ADR data in a PV database is also presented. MSs who wish to develop or improve their own procedure for quality assurance of ADR data in their database can consider this case study and checklist and use any aspects of these examples that fit the specificities of their ADR processing and of their ADR database.

3.1. Case study: MHRA procedure for monitoring and reporting on ADR data quality in the PV database

In the United Kingdom, ADR data is collected from healthcare professionals, patients and the pharmaceutical industry via the Yellow Card Scheme (YCS). ADR reports are received on a daily basis and the information provided is entered into the PV database by associate signal assessors and signal assessors in the Pharmacovigilance Information Unit of the Medicines and Healthcare Products Regulatory Agency (MHRA).

The MHRA has had an internally developed procedure for monitoring, documenting and reporting on ADR data quality in place since 2007. The quality audit of ADR data is carried out on a monthly basis with a summary report produced for the management team and the reports requiring re-classification being sent back to the assessors for reclassification. The audit only includes cases received directly from healthcare professionals or members of the public that are coded into the MHRA's ADR database by the Pharmacovigilance Information Unit. MAH reports were previously covered by a separate MHRA audit process. However, this is no longer performed, as the EMA conducts data quality activities for EV, including provision of feedback on the quality of ICSRs to MAHs and NCAs.

3.1.1.Report selection and allocation

On the first working day of a new month, a query is run to obtain a list of all initial reports of fatal and serious UK spontaneous ADR that occurred over the course of the previous month. A pre-defined number of ADR reports (usually 100 reports) are audited each month. These include a combination of all fatal reports for that month and a selection of serious ADR reports for that month, received from healthcare professionals and patients. The selection of serious reports for audit is prepared in line with an internally developed guidance sheet for details on the selection of ADR reports to audit. Only accredited signal assessors are eligible to perform the audit, having successfully passed a Vigilance Competency Framework, which includes assessment of their own data processing quality. As part of the audit, a signal assessor must not review a report they themselves have previously worked on. The signal assessors must agree with their team manager a date to conduct their audit and will subsequently be allowed to work on this in place of their usual case processing work.

3.1.2 Error classification and recording errors

Errors are categorised according to the potential impact on MHRA PV activities. There are three types of error classification, as presented in **Table 1**.

Table 1. MHRA ADR data quality audit – error categories

Type A	Type B	Type C
'Major errors' affecting ability to identify potential signals / publication of list of suspected ADRs on MHRA's website / breach of patient or reporter confidentiality	Errors affecting anonymised ICSRs sent to MAHs or provision of ADR data / the ability to accurately assess reports using signal detection software for analysis	Administrative errors – where standard procedure has not been followed and 'poor workmanship'
Examples: • Wrong report type (study instead of spontaneous) • Suspect drug name(s) omitted or wrong • Suspect reaction name(s) omitted or wrong MedDRA Preferred Term (PT) used • Fatal outcome omitted or recorded against wrong ADR • Confidentiality – patient/reporter details (excl. age and sex) in text boxes • Report seriousness status incorrect	Examples: • Suspect drug details incorrect – errors in treatment dates / dose / indication / action taken with drug • Concomitant drugs: omitted, ADR treatment entered as concomitant drug • Suspect reaction – outcome / dates / treatment • Patient details omitted/incorrect • Medical history omitted • Test results omitted • Yellow Card type – incorrectly selected (patient MHRA, industry ADR, etc.) • Council for International Organisations of Medical Sciences (CIOMS) seriousness flags omitted or incorrectly set, although not affecting report seriousness • Reporter type – incorrect (Patient / General Practitioner (GP), etc.) • Test results incorrect • Medical history incorrect • Patient permission flags set incorrectly	Examples: • Missing or incomplete reaction text. • Spelling mistakes / typographical errors / abbreviations in free text / reaction text in CAPS • Information not classified in appropriate area (treatment / medical history in reaction text rather than treatment box / patient medical history fields) • Reporter title omitted / address details not entered correctly • Medically confirmed flag not set to 'N' for patient reports • Post-mortem flag set incorrectly • Medical history flags not set • Yellow Card Centre (YCC) flag not set to 'yes' on reports from YCC regions

The signal assessor must perform quality assurance (QA) of the reports allocated to them and check that the information has been entered from the original report into the PV ADR database according to the internally developed PV Classification Guidance Manual. The details of all errors detected during the ADR data quality audit must be recorded on the internally developed QA audit spreadsheet. In addition, the details of each ADR report audited must be recorded on the QA audit spreadsheet, even if there were no errors detected in the report.

Once all reports have been audited, the signal assessors, team managers, Pharmacovigilance Information Unit Manager and/or Quality Standards Manager meet to discuss and agree on the results and resolve any questions that arose during auditing.

3.1.3 Calculating QA audit results and the Quality Audit Monthly Report

Once all the ADR reports in the monthly sample have been audited, and the details have been recorded on the QA audit sheet, the statistics for the reports are calculated from the results. The total number of errors for each category and the percentage of reports with Type A, B and C errors is then calculated.

After each audit of ADR data, the calculated results are displayed and analysed in a report for discussion. There is an internally developed template for this report. This Monthly Quality Audit Report contains sections on results of the audit, discussion on the errors (with a focus on Type A errors) and recommendations for improvement.

Specifically, the results section contains the following information:

- Sample size
- Cumulative error frequency
- Distribution of errors
- Causes of errors
- Distribution of type of errors between electronic and paper reports.

Information on sample size includes the number of fatal reports, the number of serious healthcare professional reports and the number of serious patient reports. Information on error frequency contains data on the percentage of reports according to the error type, for the past six months, presented as a figure. Distribution of errors is presented, with number of reports according to error combinations, as a table, a narrative and as a figure. The causes of errors are categorised as difficulty in interpreting the information in an ambiguous report, omission of information present in the original report and procedural errors; these are presented as a narrative and as a figure, as per error type categories. Distribution of type of errors between electronic and paper reports is presented as a narrative and a figure.

Once the report has been agreed amongst all signal assessors and team managers, it is sent to the senior management team for review.

3.1.4 Feedback, reclassification and review

All reports containing type A and type B errors are reclassified to rectify these errors. Team managers cascade the reclassification emails to the relevant assessors who were involved in the data capture, QA and Commit steps of the reports. These emails contain information about which reports need to be reclassified and what information needs to be changed. Assessors must then reclassify reports within a week of receipt of the reclassification email.

The monthly QA audit report is discussed in management meetings and team meetings to review quality trends over the past 12 months and to identify opportunities for improvement in error rates. The report is also cascaded to all assessors via email along with a short summary of key errors identified and recommendations for best practice in coding these errors. Issues identified from the QA audit, which would benefit from clearer guidance on these topics, are updated in the Classification Guidance Manual on a regular basis. Other initiatives undertaken in response to QA audit results include quality workshops with signal assessors and training sessions for individuals based on their specific performance results. Results are also fed into the Vigilance Competency Framework for associate signal assessors who are working towards their accreditation and are reviewed with all assessors as part of their six-monthly performance appraisal cycle.

3.2. Checklist for defining internal procedure for quality review of ADR data in a PV database

A brief checklist, which MSs who plan to establish or improve their own internal procedure for quality review of ADR data in their database may take into consideration, is presented below.

Steps for Defining Internal Procedure for Quality Review of ADR Data in a Pharmacovigilance Database:

1. Define the aim/purpose, scope, responsibilities for and frequency of performing the ADR data quality review procedure
2. Define the criteria for selecting the sample of ICSRs for review (e.g. in terms of type and number of reports)
3. Define error classification and additional references to be used for reviewing the ICSRs (i.e. relevant external guidelines, such as MTS:PTC)
4. Develop guidance for reviewers, taking into account the error classification and relevant references
5. Define the process of allocation of reports and the timelines for review
6. Define how the decision on classification of error and/or overall quality review is made (e.g. whether the findings are discussed between quality reviewers or a single reviewer is making the decision)
7. Define the types of recommendations for improvement (e.g. corrections of ICSRs, individual feedback to assessor, IT interventions on the database, education for all assessors, etc.); you may link them to error classification
8. Develop templates for recording the errors and the overall review; make sure that the template for the report contains an area for recommendations for improvement
9. Define how the report results are fed back to assessors, including timelines and responsibilities
10. Define how corrections to the ICSRs and other recommended improvements are implemented and reviewed, including timelines and responsibilities
11. Describe the entire process in an SOP and, if applicable, in Work Instructions (WI) and other supportive documents.

4. Supplementary tools

MSs can use other tools to supplement the insights gained from the internal procedure for quality review of ADR data in their database. These tools differ in their aims and scope, so this should be taken into consideration. Supplementary tools presented in this document are:

- EudraVigilance (EV) Feedback Report
- vigiGrade completeness score
- The Clinical Documentation tool (ClinDoc).

4.1 EudraVigilance feedback report

4.1.1 Overview

The EMA routinely monitors the quality of data transmitted electronically to EV by MAHs and NCAs. The main emphasis of this quality review is put on aspects that cannot be checked automatically based on the EV business rules. The business rules check for most inconsistencies in the structured data, which means the quality review process is only needed for unstructured data. Since the EMA rarely has any source documents to check the ICSRs against, the ICSR data quality checking relies on accurate population of the fields. The literature cases are an exception in that the published literature articles can be used as the source for data quality checks.

The review consists of three important aspects:

- Data quality review of the content of ICSRs
- Recoding of medicinal product information provided in ICSRs
- Identification of potential duplicate cases.

The data quality review process is carried out by selecting a set of ICSRs sent in by the organisation being reviewed. The review focuses on case documentation, the application of coding principles in accordance with current ICH guidelines and points to consider documents and adherence to expedited reporting timelines. A report is provided summarising the review, its outcome and potential findings, including a list of suggested actions for improvement, where applicable. The organisation under review is requested to review the report and is invited to send their comments back to the EMA. If the findings on an ICSR require corrections that would lead to significant changes that will impact the medical interpretation of the case, a corrected follow-up version should be submitted to EV as soon as possible. Medical judgement should be used for assessing this. In addition, corrected follow-ups should be submitted if additional information or changes to administrative information have been identified that could impact case management, e.g. other case identifiers have been identified but not provided in the correct data fields.

The process of ICSR data quality checking is described in an SOP and accompanying Work Instructions (WI). The SOP defines the purpose, scope, responsibilities, changes since last revision, documents needed for this SOP, related documents, definitions, process map/flow chart, procedure and records. The WI provide details on how to perform the data quality review. An additional WI provides details on organising EV reporting review meetings with organisations that are to subject review. **Figure 4** shows a flow chart of the EV ICSR data quality checking and is followed by a description of the process.

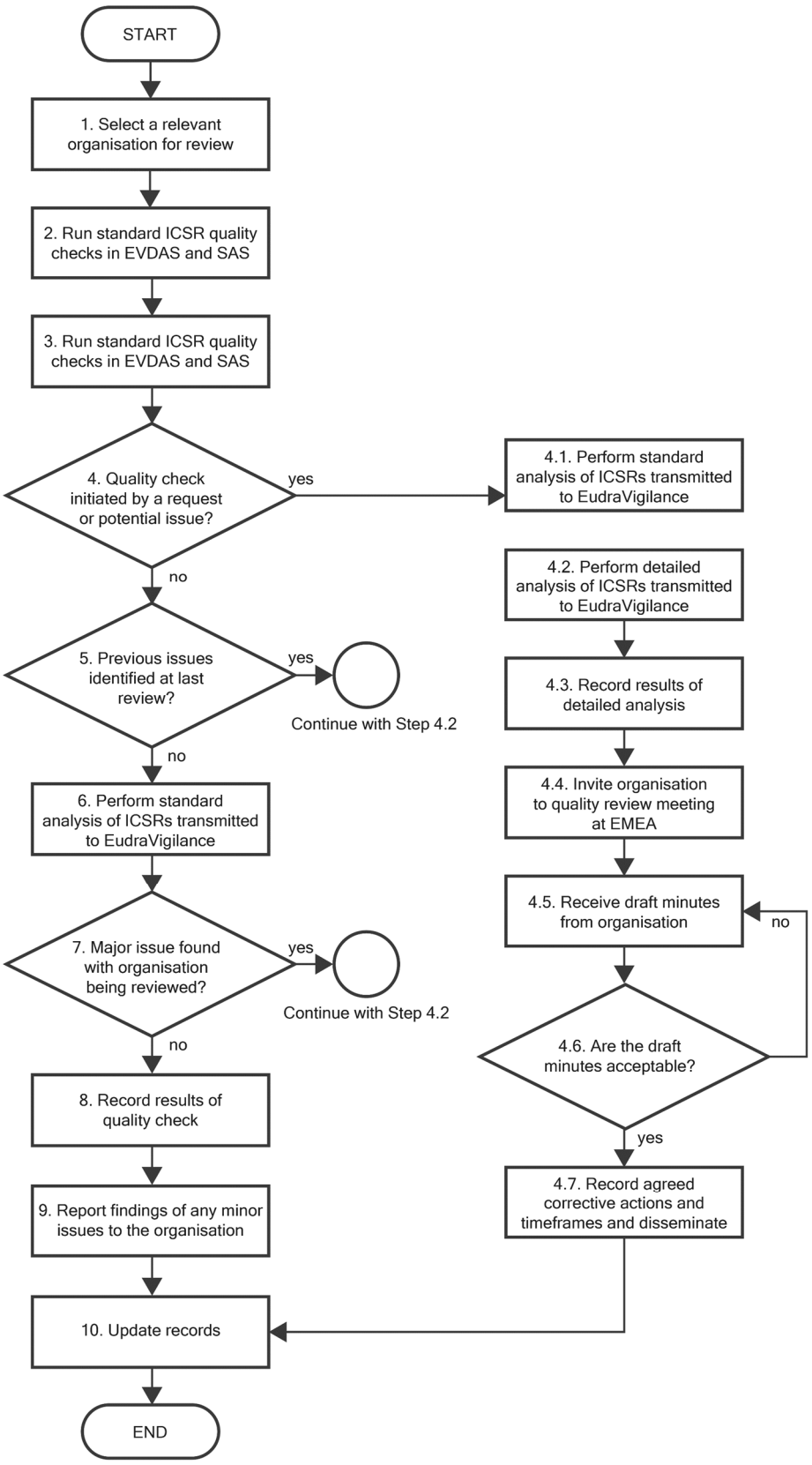

Figure 4. Flowchart of the EV ICSR data quality checking

4.1.2 Prioritisation for review

Every six months, a standard ICSR quality check in the EudraVigilance Data Analysis System (EVDAS) and a Statistical Analysis Software (SAS) query are run on the entire EudraVigilance database for the period since the last run and the outputs are stored in the EMA's electronic document management system. The output ranks the organisations, taking into account numbers of errors and numbers of ICSRs, and this ranking is used to inform the prioritisation for checking each organisation. If applicable, the outcomes of previous quality review meetings with an organisation and whether or not there have been any specific concerns raised about an organisation are taken into account. These concerns can include, but are not limited to, issues raised by NCAs, issues detected during routine PV at the EMA, an organisation implementing a new PV system or organisations merging. Based on the described prioritisation procedure, 10 reports are being produced each month for organisations that send reports to EV (i.e. MAHs and NCAs). There are no specific timeframes for producing the reports for any given sender.

4.1.3 Quality review of ICSRs

After the organisation to be reviewed is selected, standard ICSR quality checks in EVDAS and SAS, containing a number of pre-defined queries designed for the purpose of checking the quality of ICSRs, are run. In addition, there are pre-defined queries available for tracking other issues, such as expedited reporting compliance and the nullification of individual cases.

When analysing the results of the EVDAS and SAS queries, it is taken into account if the quality check was initiated by a request or because of a potential issue and if previous issues were identified at last review. If an answer is yes to either of these questions, a detailed analysis of ICSRs transmitted to EV is performed; if answer is no to both questions, a standard analysis of ICSRs is performed. If a major issue is found with the organisation being reviewed in a standard analysis, a detailed analysis is performed. A request for an ICSR data quality review can be submitted by the organisation concerned, any sector or unit of the EMA dealing with medicinal products for human use or the PV/clinical trial department of any NCA in the European Economic Area (EEA). A potential issue refers to quality aspects that are identified during routine PV activities, PV inspections, as part of the internal quality review process of the organisation concerned, the EMA or an NCA in the EEA.

Selection of the cases for review is performed as per internal document Selecting Cases for Review. 10-15 recent cases are selected for review, usually from the last 2-3 months, to reflect the current situation with the ICSRs from an organisation. The focus of the selection is on specific, potentially problematic cases, including parent-child cases, Suspected Unexpected Serious Adverse Reactions (SUSARs), cases from observational studies and fatal cases. Both cases from clinical trials and post-marketing cases are represented in the review. Review of the fields completed by the organisation is guided by an internally developed ICH E2B(R2) field guide titled Detailed instructions on checking each field of the ICSRs.

Specifically, the case narratives and free text fields are checked for any information that should be provided in the structured fields. Thus, the cases are checked to see if they are internally consistent and correctly coded. In particular, the following information is checked:

- Structured tests
- Structured medical and drug history
- Dosage structuring
- Drug substance and medicinal product names
- Indications
- Reaction outcomes
- Seriousness flags
- Reactions.

The structuring is compared against GVP Module VI and particularly against the MTS: PTC to ensure correct coding of the reactions and other medical terms. Due attention is also given to correct coding of the medicinal product and active substance names, because these are some of the most important fields for signal detection and are at high risk of being populated incorrectly. For this aspect of review, an internal document titled Examples of incorrect population of drug substance and medicinal product information is used as guidance.

The errors identified in the review of the quality of ICSRs are classified as major or minor, as presented in **Table 2**.

Table 2. Classification of errors identified in the EV ICSR data quality checking

Major error	Minor error
A major error is a systematic issue that would have a detrimental impact on the pharmacovigilance assessment of a medicinal product's safety profile.	A minor error is a non-systematic issue (i.e. one found in only one or two cases) or a systematic issue that does not significantly impact upon the pharmacovigilance assessment of a case or the reporting compliance monitoring.
Major issues include, but are not limited to: • Late reporting – if an organisation has a significant percentage of reports transmitted to EudraVigilance later than 7 or 15 days, as applicable • Incorrect coding of reaction terms • Failure to set the correct seriousness flags	Minor issues include, but are not limited to: • Incorrect patient weight • Incorrect patient height • Incorrect population of B.4.k.2.1 with the INN

4.1.4 Results, quality review meetings, corrective actions and records

The results of the analysis are recorded in the report titled Detailed ICSR Data Quality Review Summary Report. Electronic copies of the reports are saved in the general Quality Assurance (QA) checks folder, with a copy being linked to the appropriate organisation folder, both in the EMA's electronic document management system. A summary of the overall findings is also entered into the EudraVigilance ICSR Quality Checking Spreadsheet in the EMA's electronic document management system.

If no major issues are found in a standard analysis of ICSRs, the results of the quality check are recorded as described above and the findings are reported to the organisation. If any major issues were identified in a standard analysis or if a detailed analysis was performed, the results are recorded as described above and an organisation being reviewed can be invited to an ICSR quality review meeting at the EMA. The meeting is organised as per respective WI.

The organisation under review is responsible for drafting the official minutes of the meeting. The minutes should include the proposal of corrective actions and timeframes and should be prepared and submitted to the EMA for approval within two weeks following the meeting. The minutes are reviewed by the staff member(s) who attended the meeting for accuracy and acceptability and are then passed upwards for review and approval. The EMA should confirm within two weeks if the draft minutes are accurate and the proposed corrective actions and timelines acceptable. If they are not, then the comments are sent to the organisation for incorporation in the minutes.

The minutes containing the agreed corrective actions and timeframes are stored in the EMA's electronic document management system. A summary of the overall findings is also entered into the EudraVigilance ICSR Quality Checking Spreadsheet. The spreadsheet serves the EMA to monitor the agreed actions and timelines.

4.2. vigiGrade completeness score

The vigiGrade completeness score is a tool developed by UMC in order to measure the amount of clinically relevant information in an ICSR from VigiBase[14,15,16]. This tool identifies well-documented ICSRs and is able to highlight systematic data quality issues. A completeness score is calculated for each ICSR, but is usually given as an average number for all ICSRs submitted from one country over time. vigiGrade is measuring structured data without reflecting whether the information establishes causality between the drug and the ADR. The score can range from 0.07 to 1 and is calculated from several field scores by a multiplicative model. Completeness is first computed for every reported drug-reaction pair. In cases of more than one drug-reaction pair inside the ICSR, values are aggregated to an average to yield a score for the ICSR.

The vigiGrade completeness score reflects the ten dimensions of an ICSR, as presented in **Table 3**. In case of missing information, a corresponding penalty factor is applied.

Table 3. Dimensions of vigiGrade completeness score

Dimension	Description	Considerations	Penalty
Time to onset	Time from treatment start to the suspected ADR	Imprecise information penalised if there is ambiguity as to whether the drug preceded the adverse event, with 30% if the uncertainty exceeds 1 month, 10% otherwise	50% 30% 10%
Indication	Indication for treatment with the drug	Penalty imposed if information is missing or cannot be mapped to standard terminologies, such as the International Classification of Diseases (ICD) or MedDRA	30%
Outcome	Outcome of suspected ADR in the patient	'Unknown' treated as missing	30%
Sex	Patient sex	'Unknown' treated as missing	30%
Age	Patient's age at onset of the suspected ADR	Age 'unknown' treated as missing. 10% penalty imposed if only age group is specified	30% 10%
Dose	Dose of the drug(s)	Penalty imposed if the total daily dose cannot be calculated from the included fields	10%

[14] Bergvall T, Norén GN, Lindquist M. vigiGrade: A tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Safety, 2014, 37(1):65-77.

[15] Technical description of vigiGrade completeness score

[16] vigiGrade Product Leaflet

Dimension	Description	Considerations	Penalty
Country	Country of origin	Supportive in causality assessment since medical practice and adverse reaction reporting vary between countries	10%
Primary reporter	Occupation of the person who reported the case (e.g. physician, pharmacist)	Supportive in causality assessment, since the interpretation of reported information may differ depending on the reporter's qualifications. 'Unknown' penalised as missing information, whereas 'Other' is not penalised	10%
Report type	Type of report (e.g. spontaneous report, report from study, other)	'Not available to sender (unknown)' treated as missing	10%
Comments	Free text information	Uninformative text snippets excluded	10%

The dimensions and their associated penalty factors were determined by three UMC PV experts with medical training, through consensus, to match the relative importance of each dimension to causality assessment. Three levels of importance were distinguished:

- Essential (information without which reliable causality assessment is impossible)
- Important (information without which reliable causality assessment is very difficult)
- Supportive (information that is valuable, but without which causality assessment can still typically be performed).

The penalties for missing information are the same across each level of importance. An example of how the vigiGrade completeness score is calculated for an ICSR is shown below in **Figure 5**.

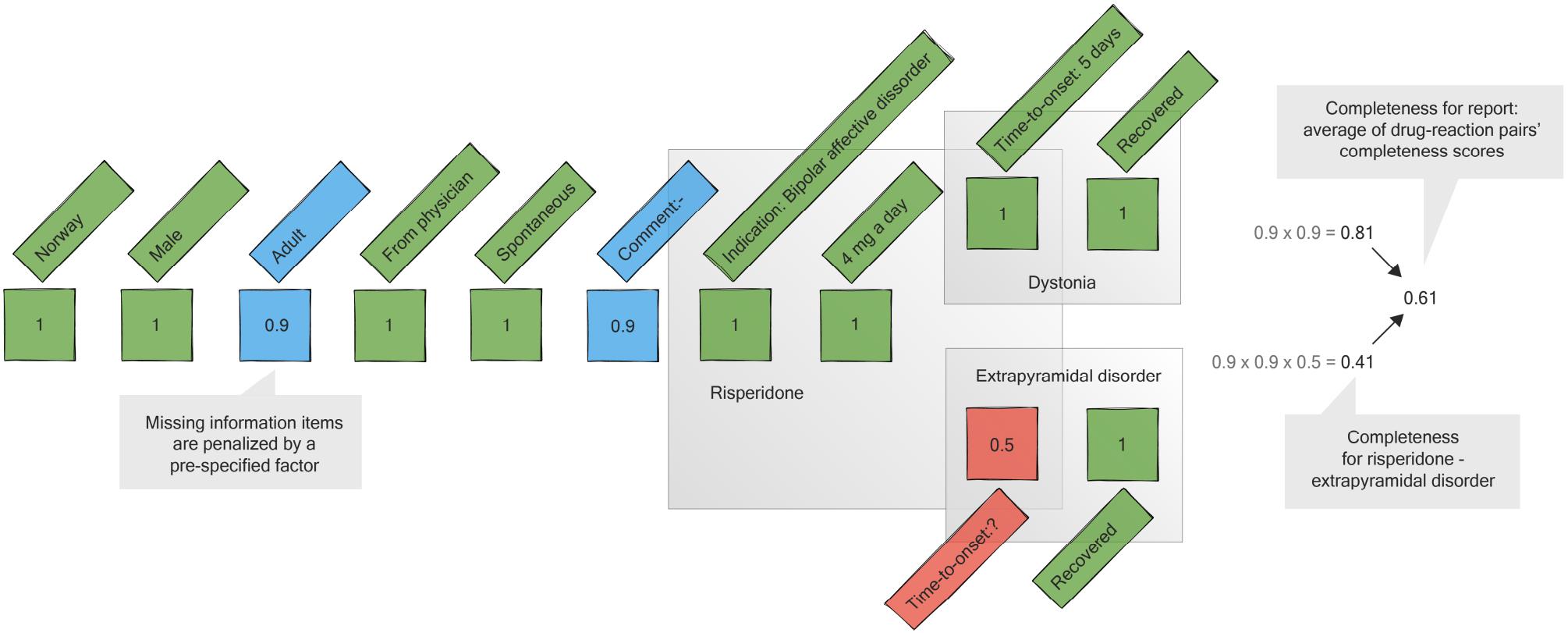

Figure 5. Example of how the vigiGrade completeness score is calculated for an ICSR

A completeness score is calculated for each ICSR, but is usually given as an average number for all ICSRs submitted from one country over time. This average number can then be further analysed and compared amongst countries and time intervals. A sudden unexpected drop in the score can be indicative of possible systematic errors when submitting reports to VigiBase and should be further addressed.

A study was performed in order to analyse reports in VigiBase from 2007 to January 2012[17]. For the purpose of this study, all reports with scores >0.8 were considered as well-documented. For VigiBase as a whole, the median completeness was 0.41, with an interquartile range of 0.26–0.63. Two out of three well-documented reports came from Europe, and two out of three from physicians. The results showed that among the countries with more than 1,000 reports in total, the highest rate of well-documented reports is 65% in Italy. Tunisia, Spain, Portugal, Croatia and Denmark each have rates above 50%, and another 20 countries have rates above 30%.

The two examples below show how vigiGrade can be used to discover certain systematic errors:

1. A lower than expected completeness for reports from Italy was observed in 2011. This was traced to a consistent lack of information on outcome. The issue was communicated by UMC to the Italian authorities who resubmitted all their reports with the outcome information included. As a result, Italian reports as represented in VigiBase at the time this article was prepared, were the most complete for any country with at least 1,000 reports.
2. An unexpected drop in completeness for reports from the US Food and Drug Administration (FDA) was also observed in 2011. From 2010 to 2011, the average completeness decreased from 0.45 to 0.30. Subsequent analyses revealed that from 2011 onwards, the age unit format on reports from the USA did not conform to the E2B guidelines. As a result, all American reports from 2011 lacked age information in VigiBase, and none of them were classified as well documented (since missing age is penalised by 30%). This issue was communicated by UMC to the FDA and has been addressed in subsequent versions of VigiBase.

It is important to note that sometimes original reports at each national centre may contain more information than it is available in VigiBase; however, if that data is not adequately structured, or if not all data is submitted to UMC, the completeness score will be lower than expected. In the future, it can be expected that vigiGrade will improve with the development of natural language processing techniques that can extract meaning from the text.

The vigiGrade completeness score reports prepared for individual countries contain the completeness scores for ICSRs from the respective country over the past five years. A detailed description of the calculation of scores is presented for reference in the supporting document titled Technical description to vigiGrade completeness score. The report consists of six sections:

[17] Bergvall T, Norén GN, Lindquist M. vigiGrade: A tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Safety, 2014, 37(1):65-77.

- Completeness score by country – overview for all countries
- Average completeness score – for country
- Completeness score by field – for country
- Time to onset – completeness and consistency – for country
- Age at onset – completeness – for country
- Dosage completeness – for country.

Since the beginning of 2016, vigiGrade graphs can be provided for different subgroups of ICSRs, based on the E2b format. This allows comparisons of, e.g., ICSRs with company IDs and ICSRs with authority numbers. These graphs can be requested from UMC (vigibase@who-umc.org) on an ad hoc basis.

4.2.1 Documentation grading – completeness score

Documentation grading – completeness score was the predecessor of vigiGrade, also developed by UMC. Documentation grading was developed on the same principles as vigiGrade, but with some key differences:

- Documentation grading had eight dimensions: type of report, primary source, gender, time to onset, age at onset, outcome, indication and free text. vigiGrade has two additional dimensions – dosage and country.
- The names of three dimensions were changed in order to comply with ICH-E2B. Gender, free text and primary source were changed to patient sex, comments and primary reporter, respectively.
- Documentation grading had eight different levels of penalties instead of three in vigiGrade.

Results between these two tools shouldn't be compared because of different penalty levels and newly added dimensions.

4.3. Clinical documentation tool

As part of the Web-Recognising Adverse Drug Reactions (WEB-RADR) Project, the Netherlands Pharmacovigilance Centre Lareb has developed a Clinical Documentation tool (ClinDoc) in order to assess the clinical documentation of ICSRs in an international PV setting[18]. A good quality of clinical information contained in ICSRs is important for signal detection. ClinDoc was developed by five PV professionals with different professions, skills and working experience. The stages of development were: formulation of domains and subdomains for clinical documentation, face validity testing and validity and reliability testing. Eight PV assessors from four different countries performed the validity and reliability testing.

ClinDoc contains four domains, important for assessing the clinical documentation of ICSRs:

- Adverse drug reaction (ADR)
- Chronology
- Suspected drug
- Patient characteristics.

Since ADRs can be very diverse, the information required for a good clinical assessment varies depending on the type of ADR. This tool is therefore a flexible model that takes this diversity into account. The unit of analysis is an ICSR and assessment is performed case-by-case; a specific sample of ICSRs can be chosen for analysis. The assessor indicates which subdomains are relevant for assessing the clinical documentation of the specific ICSR and afterwards indicates if this information is present in an ICSR or not. The score given to each domain is the proportion of information present in relation to the information deemed relevant for assessing the report. The final score for the ICSR consists of the average of the percentages scored per domain and falls under one of the following categories: poor (≤ 45%), moderate (46% – 74%) and well (≥ 75%).

The final score gives insight in the clinical documentation grade of ICSR and can be used, together with the causality outcome, in signal detection. It is of note that, for assessing the completeness of ICSRs, ClinDoc takes the content and the relevance of the information into account, and not only the presence of information. The tool can be used to compare the clinical quality of reports, for example, between different reporting groups, such as patients and nurses, or different means/sources of reporting, such as mobile phone applications and automatic reporting from a general practitioner or hospital systems. When certain reporting methods or specific groups of reporters show poor clinical quality, efforts can be made to enhance the quality.

[18] Rolfes L, Oosterhuis I, Ekhart C, Muller-Hansma A, Härmark L: Development and testing of a Clinical Documentation tool to assess Individual Case Safety Reports in an international setting. Manuscript submitted for publication.

5. Conclusions

Within Audit of national reporting systems of the SCOPE WP4, the information about EU MS practices with regard to the use of indicators and metrics for monitoring the quality of reports in their national ADR databases was collected through a questionnaire completed by EU MSs. Results showed that only 13 out of 27 MSs use indicators or metrics and only five of those MSs use internally developed indicators that are included in SOPs and regular compliance checks or quality audits. In addition, the results of a UMC search of VigiBase for EU/EEA countries for the period 2009-2013 showed that, although the average completeness score for the EU/EEA was satisfactory and stable over time, there is room for improvement. This document containing an overview of tools was therefore prepared with the aim of supporting MSs in their efforts to continuously monitor and improve the quality of reports in their national databases.

A case study of MHRA procedure for monitoring and reporting on ADR data quality in their PV database, and a checklist for defining internal procedure for quality review of ADR data in a PV database, were presented in this document. MSs who wish to develop or improve their own procedure for quality assurance of ADR data can consider this case study and checklist and use any aspects of these examples that fit the specificities of their ADR processing and of their ADR database. MSs can also use other tools to supplement the insights gained from the internal procedure. These tools include the EudraVigilance (EV) Feedback Report, the vigiGrade completeness score and the Clinical Documentation tool (ClinDoc), which were also described in this document.

In conclusion, it needs to be reiterated that, in PV, continuously monitoring and improving the quality of data in national ADR databases is essential. Only a comprehensive tool, such as internal procedure for quality assurance of ADR data, can enable MSs to ensure the good quality of ADR reports. This can be further supplemented by using other tools presented here.