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# Working Paper: IDMP-ICSR Clinical Connectivity

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## Working paper abstract

UNICOM Task 8.4 aims to improve a core international pharmacovigilance activity: processing and analysis of individual case safety reports (ICSR) that describe one or more suspected adverse drug reactions (ADRs) that occur in a single patient. One possible intervention to improve spontaneous ADR reporting is to integrate ADR reporting functionalities in clinical systems, e.g. hospital information systems, general practitioner systems or pharmacy systems. This working paper explores the use of ADR reporting features in clinical system software, with emphasis on identifying reusable initiatives and characterising their use of medication description for suspect and concomitant medication. To this end, a survey amongst UK and EU National Competent Authorities and a tailored literature review were conducted. Using the ICSR-IDMP coding guidance developed earlier and taking into consideration the guidance for use of Identification of Medicinal Products (IDMP) in Medicinal Product Dictionaries (MPD); general recommendations are made for transformation of MPD descriptions in clinical systems to IDMP descriptions for ADR reporting in the ICSR format. Furthermore, this working paper provides general recommendations for development and implementation of spontaneous ADR reporting functionalities in clinical systems.

Keywords: Pharmacovigilance, ADR, ISO IDMP, ICSR, ICH E2B(R3), EU ICSR Implementation Guide, case processing, MPD, EHR, clinical systems

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# List of abbreviations

| Abbreviation | Complete form |
|---|---|
| ADR | Adverse Drug Reaction |
| API | Application Program Interface |
| CIOMS | Council for International Organisations of Medical Sciences |
| CSV | Comma Separated Values |
| DKMA | Danish Medicines Agency |
| Dm+d | Dictionary of Medicines and Devices (United Kingdom) |
| EC | European Commission |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| EU | European Union |
| EU-SRS | European Substance Registration System |
| GP | General Practitioner |
| G-SRS | Global Substance Registration System |
| GVP | Good Pharmacovigilance Practice |
| HALMED | Agency for Medicinal Products and Medical Devices of Croatia |
| HCP | Healthcare professional |
| ICH | International Council for Harmonisation |
| ICSR | Individual Case Safety Report |
| ID | Identifier |
| IDMP | Identification of Medicinal Products |

| | |
|---|---|
| INN | International Non-proprietary Names |
| ISO | International Organisation for Standardisation |
| JAZMP | Agency for Medicinal Products and Medical Devices of Slovenia |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board (The Netherlands) |
| MedDRA | Medical Dictionary for Regulatory Activities (MedDRA® trademark is registered by ICH). |
| MHRA | Medicines and Healthcare products Regulatory Agency (United Kingdom) |
| MPD | Medicinal Product Dictionary |
| MPID | Medicinal Product Identifier |
| NCA | National Competent Authority |
| NHS | National Health Services (United Kingdom) |
| PCID | Packaged Medicinal Product Identifier |
| PhPID | Pharmaceutical Product Identifier |
| PhV | Pharmacovigilance |
| PMS | (EMA) Product Management Service |
| RMS | Risk Management System |
| SID | Substance Identifier |
| SNOMED CT | Systematized Nomenclature of Medicine Clinical Terms |
| UCUM | Unified Code for Units of Measure |
| WHO-UMC | World Health Organisation - Uppsala Monitoring Centre |
| XEVMPD | EudraVigilance eXtended Medicinal Product Dictionary (also known as art 57 database) |
| XML | Extensible Markup Language |

# 1 Executive summary

UNICOM Task 8.4 aims to improve a core international pharmacovigilance (PhV) activity: processing and analysis of individual case safety reports (ICSR) that describe one or more suspected adverse drug reactions (ADRs) that occur in a single patient. Integrating ADR reporting functionalities in clinical systems is mentioned as a possible improvement to tackle the well-known issue of underreporting with spontaneous reporting systems. This working paper explores the use of ADR reporting features in clinical system software, with emphasis on their use of medication description for suspect and concomitant medication in ISO IDMP identifiers.

For this purpose a survey amongst UK and EU National Competent Authorities and a tailored literature review were conducted. The NCA survey identified 11 countries with relevant initiatives, describing different levels of integration: from incorporating a link to the online ADR reporting webform of the NCA, to a fully integrated dataflow using information from the clinical system. Information on medications can be transmitted from clinical systems as drug verbatims with varying levels of precision. Most likely this transmission will use the identifiers and descriptions for medication from a local or national patient care medicinal product dictionary, which will then require mapping to the PhV medication dictionary. Overall, the principles described in UNICOM Working paper 8.7 can be applied for transforming these drug verbatims into IDMP identifiers. Ideally, IDMP identifiers will be made available via the clinical systems in the future. Also then, depending on the level of information available in the drug verbatim, ICSR 'name part data elements' still need to be populated.

Since information in clinical systems is collected primarily to manage the patient and for administrative purposes, it does not necessarily meet the standards for ICSR reporting. The special situations described in section 6.2 (e.g. medication error, interactions and parental exposure) highlight that ADR reports received from clinical systems may need careful attention when entering in PhV databases to ensure that the ICSR Drug Section will be populated correctly. Although the ICSR does not have a data element for Package Identifiers it may be useful to explore transmission of the IDMP PCID or nationally defined package identifiers when reporting an ADR to a PhV centre. These package identifiers could then subsequently be used to retrieve other identifying drug information that fit with the ICSR drug data elements (MPID, name parts).

Just having a technical solution in place does not necessarily lead to more ADR reports being sent to the PhV centre, as it all starts with recognizing ADRs and documenting these in clinical systems. To improve documenting ADRs in the patient record, the design should follow a logical implementation in the clinician's workflow, preferably in a standardized way. This would also allow clinicians to build familiarity with the system and the data, regardless of the setting in which they are working. The UK appears most successful with their integrated Yellow Card strategy and has been highlighted as a best practice. Their strategy is based on four pillars (education, promotion, facilitation and motivation) and involves all relevant stakeholders. Finally, if integrating ADR reporting functions in the clinical system provides difficulties, other mechanisms should also be considered to improve PhV reporting using the available information in clinical systems.

# 2 Introduction

## 2.1 Background

Pharmacovigilance (PhV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The European Union (EU) PhV system is underpinned by a legal framework (Regulation (EC) No 76/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012) that establishes roles and responsibilities, principles and procedures for the regulatory network (national competent authorities: NCAs, European Medicines Agency: EMA, and European Commission: EC) and pharmaceutical industry (referred to as Marketing Authorisation Holders: MAHs).

Safety monitoring through collection and analysis of suspected adverse drug reaction (ADR) reports is a cornerstone of PhV. Reports of suspected ADRs are initially collected by MAHs and NCAs (or their regional/national PhV centres) and originate from a variety of sources, including healthcare professionals (HCP), patients/consumers and medical literature. Onward exchange of suspected ADRs is based on legal requirements and involves a large number of stakeholders worldwide. Gathering suspected ADRs into international PhV databases as Individual Case Safety Reports (ICSRs) facilitates the detection of drug safety signals – which might not be apparent from the data of a single country, and increases the probability of detecting rare ADRs.

### Difference between ADR records, reports and ICSRs

For further understanding throughout this working paper it is important to underline that there is a difference in ADR records, ADR reports and ICSRs. Clinical patient care literature mostly focuses on the recording (documenting) of (suspected) ADRs whereas the pharmacovigilance domain deals with (suspected) ADR reporting. What could appear to be a pedantic difference in semantics is actually a clear paradigm difference:

- In patient care, a clinician is presented with a patient with a clinical issue whose signs and symptoms are diagnosed to be due to an unintended and therefore unwanted harmful or potentially harmful response to a medicinal product. An ADR is therefore a diagnosis in patient care and (ideally) recorded as such in the patient's record (EHR). This diagnosis will use the (data) format that the particular EHR system requires. This information may also be shared with other care providers for this patient and will flow between patient care systems as a record of an ADR.

- It is only after this clinical process of diagnosing and recording of the ADR has completed that the clinician may then make a decision about whether or not to submit an ADR report to a PhV centre. The report from the clinician to the PhV centre can have any format (phone call, standardised webform, or a proprietary format that the EHR will provide, etc) and this will flow as a (case) report of an ADR.

The difference between a record and a report is that the systems involved are different, the data requirements are different, and the philosophy that underpins the recording of the data is fundamentally different. Despite this difference it is essential that data about (suspected) ADRs flows from patient care to PhV centres, because this is one of the cornerstones of post-marketing surveillance of medicinal products.

Managing these two flows, with their different purposes, triggers, data elements and systems, means managing two different paradigms. This challenge is shown by the Adverse Event work that has been ongoing in the Health Level 7 (HL7) organisation over 15+ years – as documented in their work products at https://confluence.hl7.org/display/PC/Adverse+Event+Topic. This is now also being facilitated by the HL7 Vulcan Accelerator, whose aim is to connect clinical research and healthcare by the implementation of HL7 FHIR standardized data exchange; their information is documented at https://confluence.hl7.org/display/VA/Adverse+Events.

- The ICSR refers to the format for the exchange of ADR reports between regulators (NCAs, PhV Centres), WHO, clinical trial sponsors and marketing authorisation holders. The ICSR therefore has a different flow, different triggers (based on legal obligations) and is totally within the regulatory PhV domain. Although the flow from clinical systems to PhV centres may be based on the ICSR format, it is unlikely that all 271 ICSR data-elements are available. By international convention, when exchanging ICSRs of spontaneous ADR reports, these are regarded as having 'implied causality'. They are commonly referred to as reports of ‘suspected ADRs' since they convey the suspicion of the reporter who takes the initiative to contact a PhV centre.

### Use of ICSR message and IDMP

As from 30 June 2022, MAHs and EU regulators are required to use the International Organisation for Standardization (ISO) ICSR 27953-1 (2011) standard for the submission of suspected ADR reports to EudraVigilance (in line with Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012). The modalities on how to implement and apply the ISO ICSR standard are defined in the International Council for Harmonisation (ICH) E2B(R3) documentation. This ISO ICSR message in ICH E2B(R3) format is also used for the exchange of ADR reports between the EMA and WHO-UMC. Conceptually, the ICSR can be considered a standard format that is capable of accommodating direct database-to-database transmission to describe one or more suspected adverse reactions to a medicinal product that occurred in a single patient at a specific point in time. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect medicinal product. This ISO ICSR message in ICH E2B(R3) format has placeholder data-elements for providing information on the medicinal product(s) in line with ISO standards for the Identification of Medicinal Products (IDMP).

UNICOM Working paper 8.7 provides coding guidance and principles for the accurate and consistent representation of drug information about medicines (including vaccines) involved in the suspected ADR in the ICSR messages. The working paper focuses on Medicinal Product Identifiers (MPIDs) and Pharmaceutical Product Identifiers (PhPIDs) (with or without name parts) that will result from the

implementation of ISO IDMP standards. General considerations are provided for selecting MPIDs and PhPIDs as well as guidance and considerations on more specific topics such as the use of context, historic identifiers and name parts.

Until the relevant IDMP terminologies and identifiers become available and are agreed for use in the ICSR message, free text can be used in the ICSR to describe medicines, both for the suspect product and for any concomitant medications. However, PhV analysis is hampered by the use of free text, lack of standardisation and exchange of medicinal product information between systems and across jurisdictions. In addition, it takes valuable resources to match medicinal products and active substances provided as free text in ICSRs to the different drug dictionaries that are used in PhV databases.

Figure 1 illustrates the exchange of EU ICSRs between NCA/PhV centres, EMA, pharmaceutical industry and WHO-UMC with use of different drug dictionaries in their respective PhV systems. The EMA uses the Extended EudraVigilance Medicinal Product Dictionary (known as XEVMPD or "Art57 database") whereas WHO-UMC uses the WHO Drug Dictionary (WHO Drug). Pharmaceutical industry may use their own internal dictionary. Furthermore, it is known that NCAs or their PhV centres use different drug dictionaries, sometimes even a drug dictionary that is used in the clinical domain. This necessitates the conversion of ICSR data from one drug dictionary terminology to another.

Additional information on the interplay between IDMP identifiers, name part data elements and ICSR messages can be found in Appendix A.

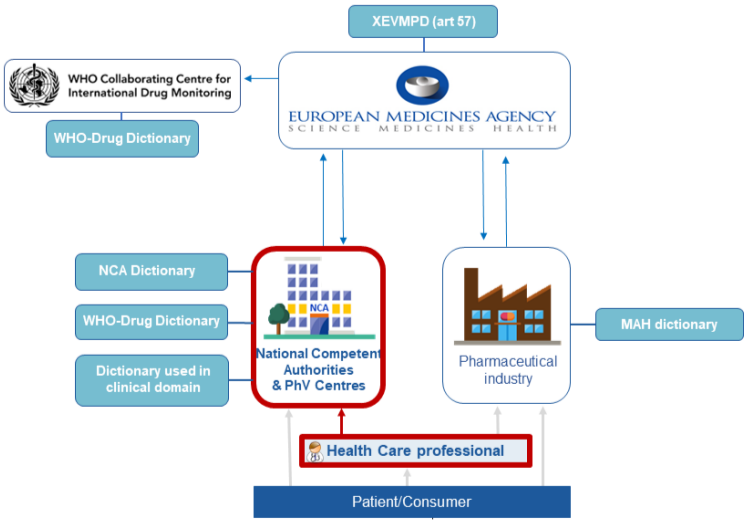



*Figure 1. Flow of ICSRs and different Drug Dictionaries used*

Blue arrows indicate exchanges in ICSR format. Patients and Health Care professionals can report suspected ADRs to NCAs/PhV centres or pharmaceutical industry via various means, for example webforms, phone, apps, et cetera. This working paper focusses on the ADR reporting from HCPs (and patients) to the NCAs as indicated in the figure with red lines.

### Improving ADR collection via IT systems used in clinical care

Underreporting is a known criticism of spontaneous reporting systems described above, with estimates that more than 94% of ADRs are not reported by HCPs (Hazell, 2006). There are many barriers to ADR reporting and reasons behind underreporting, which have been highlighted through numerous studies (Garcia-Abeijon, 2023). Examples of these barriers are inadequate IT-systems, expenditure of time by the HCPs and overall complexity of ADR reporting. Capturing and reporting ADRs also highly depends on the awareness and facilitation of reporters.

The issue of underreporting should be placed in the context of the purpose of a spontaneous reporting system. As addressed in Council for International Organisations of Medical Sciences V (CIOMS V, 2001), the principle purpose of a spontaneous reporting system is to generate signals that may lead to the identification of previously unrecognized, suspected ADRs. These systems were not designed for, nor are they intended to be, complete collections of every adverse event that occurs to a person taking a drug. A reason for not reporting could be that the ADRs is already described in the Summary of Product Characteristics and Patient Information Leaflet (Sandberg, 2022).

One possible intervention to improve spontaneous ADR reporting is to integrate ADR reporting functionalities in clinical systems, e.g. the hospital information system, general practitioner or pharmacy systems. Addition of a reporting module to the physicians' prescription system has been proven effective in several studies and is for example implemented in the UK through the Yellow Card Scheme. Within the overall report of an ADR, information about suspected and concomitant medications is pivotal. As the implementation and adoption of ISO IDMP standards is ongoing in PhV as well as in the clinical domain, there is a need to explore this reporting data-exchange and the future role of ISO IDMP identifiers.

## 2.2 Objective and scope

This working paper explores current initiatives for ADR reporting from clinical systems and provides a gap analysis between the minimum requirements for suspect and concomitant medication descriptions using IDMP in the ICSR report, and what is available from the clinical systems. The use of ADR reporting applications in clinical system software in EU member states is explored, with emphasis on identifying reusable initiatives and characterising their use of medication description for suspect and concomitant medication. Using the ICSR-IDMP coding guidance developed earlier in Working paper 8.7, and taking into consideration the guidance for use of IDMP in MPD (Working paper 9.2), recommendations are made for the transformation of MPD descriptions in clinical systems to IDMP descriptions for ADR reporting in ICSRs.

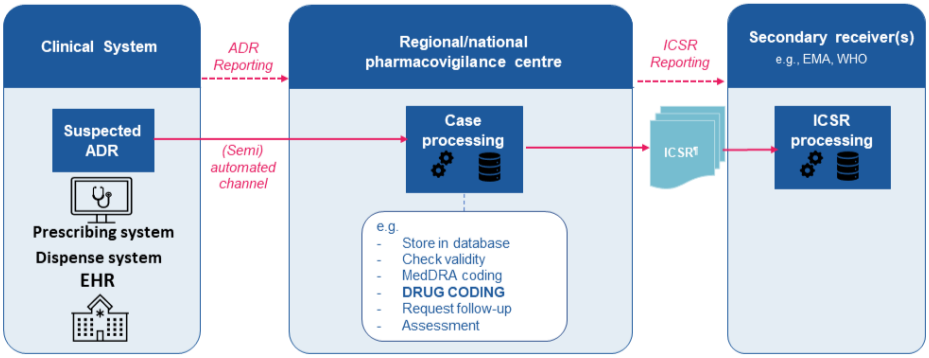



*Figure 2: Flow of (suspected) ADR reports to PhV Centres via clinical system(s) and onwards transmission in ICSR format*

The scope of this working paper is the use of clinical systems to facilitate (semi) automated spontaneous ADR reporting to PhV systems run by (or on behalf of) NCAs. This excludes:

- Adverse event reporting in the context of a clinical trial.
- The use of Electronic Health Record (EHR) datamining for PhV safety studies: EHRs allow for the passive surveillance of drug safety concerns through the mining of information that exists within the EHR.
- Other initiatives for collecting ADR reports from systems used in clinical setting, without integrated (or semi-automated) solutions for ADR reporting (e.g. where an NCA has an agreement in place with a Poison Centre to receive ADRs that occur in the context of an overdose, but files are exchanged in such a way that the case needs to be manually entered in the PhV database).

Using the WHO-UMC PhV cycle for illustration, the scope of this working paper is limited to the 'report' and 'collect' aspects (Figure 3).

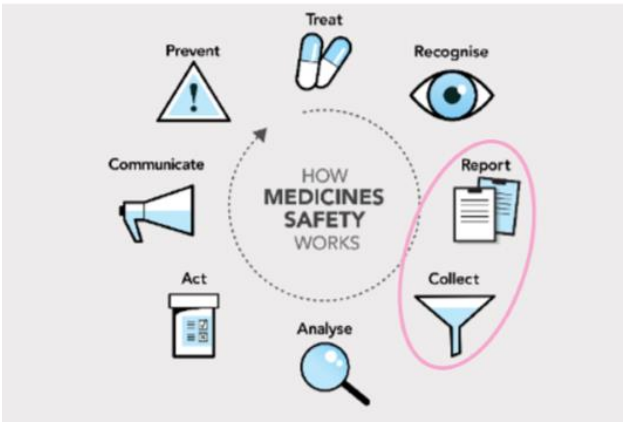



*Figure 3: WHO-UMC PhV cycle*

# 3 Methods

## Literature search

There are many published articles addressing various scientific aspects of ADR reporting. The main aim of this tailored review is to identify those publications with potential useful tools and ideas relevant for the flow of suspected ADR data from clinical systems to PhV systems in the European regulatory setting. Therefore this review does not provide a meta-analysis or a comprehensive review of all literature in this area. Using standard literature searching practices, with search terms including “adverse drug reaction”, “adverse drug reaction reporting systems” and “electronic health record system”, thirteen papers with relevant content were found and have provided the input for the discussion in section 4. In particular those publications that provide context to the scope of this working paper are highlighted, thereby excluding literature about the mining of information from EHRs, either from their structured data or from any unstructured clinical narratives which could then be used in the context of drug safety surveillance.

## NCA survey

To explore current initiatives for ADR reporting from clinical systems, EU and UK NCAs were requested in May 2022 to indicate if such initiatives are in place in their countries, and if these initiatives are operational or in development (round 1 NCA survey). Responses could be submitted until end of June 2022. NCAs that indicated to have such systems operational or in development received a follow-up questionnaire (round 2 NCA survey) to provide more detailed information for the following five types of clinical systems: general practitioner (GP) system, pharmacy system, hospital system, patients own digital health environment and the risk management system (RMS). The follow-up questionnaire was sent April 2023 and the last response was received June 2023. This questionnaire focused on the level of precision of medication identification or description for suspect and concomitant medication in these clinical systems and subsequent medication coding in line with the ICSR-IDMP coding guidance. Additional topics were also included to retrieve sufficient information regarding the ADR reporting mechanisms in these systems to assess the impact and to identify success factors and barriers of reporting via these systems.

This questionnaire tried to capture a very diverse environment with a limited set of simple questions. It is possible that it did not fully capture existing variation in recording practices that may occur for different products. For example, recording of the brand name may occur when a biosimilar is available and only a non-proprietary name is recorded if no biosimilar is on the market. However, we believe that the responses provided a sufficiently robust overview of the recording practices in the clinical care systems to support this working paper.

Although we refer to countries in general, this should not be interpreted as national coverage as initiatives can also be regional or institute specific. This should be considered while interpreting the results.

The results from the literature search and NCA survey are described in section 4 and 5. General considerations for the selection of IDMP identifiers were formed from these analyses and are presented in section 6, while other recommendations resulting from these analyses are provided in section 7.

# 4 Results literature search

The literature clearly and consistently describes the underreporting of ADRs from the patient care record in the EHR system to any sort of PhV reporting system, both in individual studies and in systematic reviews, with most studies reporting underreporting to be in the order of 80-90% of all ADRs, with little difference as to whether the ADR was deemed “serious” or “severe” or not (Hazell, 2006). Indeed some have suggested the figure of what is reported is closer to 1% (Linder, 2010). This highlights that the flow of ADRs from clinical EHR systems to PhV systems is in no sense smooth, and this appears to be the situation for both primary (ambulatory) and secondary (hospital) care.

Various factors influence the decision to report an ADR to a PhV Centre, some are human factors, some are system factors. However, human factors can also be influenced by systems, and thus also considered here. For example, the study by Gahr et al (Gahr, 2021) noted that just under half of participants (German GPs) were not aware of their obligation to report ADRs. This study also cited both the complexity of and subsequently the amount of time needed to complete a report as negative factors for reporting; both of these could be lessened by having the system pre-populate the report using data from the EHR. In addition, the human need for education and training - strongly proven by the work of Herdiero et al. (Herdiero, 2012) - indicates that having system prompts to suggest reporting could be valuable when an ADR is documented in a patient record.

To do this requires the system to have logic to detect that an ADR is being described but may not expressly named as such. A study by Khalili et al (Khalili, 2020) described this as “active surveillance” and noted that it could “significantly” increase ADR reporting.

In a study by Geeven et al (Geeven, 2022), the participants (Dutch hospital pharmacists and physicians) indicated that the factors against ADR reporting also included time constraints, but additionally directly highlighted issues with the clinical (IT) system. These issues include the inflexibility of entering data in a standard templated ADR report, and that the reporting form itself was not easy to access. Interesting to note that a positive factor for clinicians towards reporting ADRs is the feeling that this may prevent hospital (re)admission caused either directly by an ADR or by a repeating ADR. So the clinician’s focus is towards improving the care of the individual patient rather than on the public health aspect of PhV, although clinicians did acknowledge the importance of PhV and reporting ADRs to support it. There was also a sense of wanting to share an ADR report with other clinicians responsible for that patient’s care, and frustration that there was no mechanism to do this. However, paradoxically clinicians had concerns that having noted an ADR in a patient record could in the future trigger noisy alerts, such as allergy/intolerance alerts that would interfere with future workflow. Participants noted that their preference would be for a single national ADR reporting functionality which had minimal mandatory fields and which was easy and quick to complete which would allow information exchange within the healthcare sectors. Pre-population of information from the existing clinical records was not mentioned specifically, nor did they mention easier exchange with the national PhV centre.

Clearly, some further sharing and education on the requirement to and value of sharing such information with the national PhV agency should be included in any future development.

This theme of the recording of ADR for the benefit of the individual patient rather than for PhV is at the heart of a study by Skentzos et al (Skentzos, 2011), who investigated the proportion of allergic or intolerance reactions to statins that were recorded in structured data in the patient's EHR and compared it to the unstructured recording of statin side effects experienced. Unless an allergy or intolerance is recorded as structured data, it cannot be used in medication safety checking of future prescriptions for that patient. The study found that approximately only 30% of statin allergies or intolerances were being recorded as structured ADRs and although there is no indication as to whether these ADRs were then flowed on as reports to a PhV centre, it clearly highlights the problems of underreporting of adverse events occurring in the patient care setting. Suggestions for improvement in the documentation included optimising the user interface for recording ADRs and ensuring that this information was integrated to the medication module, thereby increasing the value of the data for the care of the individual patient. Similarly, work by Van der Linden et al (van der Linden, 2010) gave examples of how the absence of documentation for an ADR in the EHR system meant that individual patients suffered further serious ADR because of re-prescription of the same offending medication.

Another study, by Shchory et al (Shchory, 2020), whose primarily purpose was to establish and evaluate an intervention plan for increasing ADR reporting rate among clinicians, noted that the method preferred by its participants for making an ADR report was by telephone or using a webform. Passier et al found that GPs suggested a direct link between the GP computer system and the reporting module of the Dutch national centre to improve reporting of ADRs (Passier, 2009). Underlining the requirements for increased accessibility of a reporting tool, Chen et al (Chen, 2017) describe the effect of the addition of a reporting module to physicians prescription system in their local healthcare centre. The module allowed ADRs to be simultaneously reported as the clinician documented a drug allergy in the clinical system and was found to significantly increase the number of ADR reports made in the centre each month. The authors suggest that adding a similar module to the prescribing system would also be valuable.

A study by Durrieu et al (Durrieu, 2016) focused on the completeness of the data within the reports that were made to a French regional PhV centre, either by patients or by clinicians, using either a webform or using unstructured communications such as fax, email or letter. The main data elements for an ADR/ICSR report were studied and each report was classified as either 'well-documented', 'slightly documented' or 'poorly documented'. Only just over a tenth of the reports were assessed as 'well-documented', and these were found to be mainly reports of "serious" ADRs; interestingly, no association between report completeness and mode of ADR reporting was found, implying that unstructured reports gave as much information as structured reports. This is despite the majority of reporting "systems" offering a template for structured data capture, and particularly interesting in consideration of IDMP, which has structured medicinal product information at its heart.

Ribeiro-Vaz et al (Ribeiro-Vaz, 2012) describe how the provision of a hyperlink to web-based ADR reporting functionality has been included in the EHR system of the hospitals in northern Portugal and that this significantly increased the number of ADR reports submitted to the PhV centre, particularly for serious ADRs. Interestingly, in parallel with the increased level of reporting, there was also a significant increase in the number of visits to the website of the PhV centre, implying a raised consciousness and interest in the whole domain of PhV and ADRs from the clinicians in the area.

Ribeiro-Vaz et al (Ribeiro-Vaz, 2016) also conducted a systematic literature review focussing only on the use of information systems for the promotion of ADR reporting. The systems described a range from systems that promote ADR report submission by providing modules that facilitate the process of reporting, either within a system or separate from it, to systems that detect ADRs from within clinical data (or clinical data warehouses) and offer to the user that a report should be submitted (some pre-populating the report with available data) through to websites that actively inform healthcare professionals about ADRs. The study noted how much had changed through the duration of the study period – in particular since the start of direct patient reporting of ADRs in Europe and the trend toward web-based reporting systems which includes mobile technologies, although interventions made from inside electronic health record software clearly also have potential to improve ADR reporting. The authors endorse this approach due to its efficiency. They also noted that whilst most projects covered ADRs for all types of medication, only a few were specific, for example dedicated only to reporting vaccine ADRs. Given that this study was conducted pre-COVID-19, it is likely that there would now be more examples of such dedicated systems deployed, although this review found that the literature about ADR reporting of treatments and vaccinations for COVID-19 were understandably focused on the data itself (the ADR) rather than the systems used to gather the data.

## Conclusion

The very significant problem of under-documenting and underreporting of ADRs is widely acknowledged but very little is reported in the literature in terms of practical recommendations for technology to facilitate the information flow of adverse event information from EHRs to PhV systems. There are no studies published that focused on the reporting of medicinal products involved in the event. This is probably because there is a strong sense in EHR/patient care systems that the primary purpose of recording ADRs in these systems is for internal purposes; to safeguard the care of the individual patient rather than to flow this information on to PhV systems for clinical research and wider patient safety – despite there being a professional obligation to do so. There is a little more mention of this flow on to the PhV systems in European studies, probably because of the presence of regional (academic) PhV centres able to have more direct relationship with the patient care organisations in their area.

The most important aspects to take forward from the literature review when developing ADR reporting functionalities in clinical systems are:

- The need to pre-populate reports with data from the EHR system. Since almost all EHR systems will have medication information, this is a prime candidate for pre-population.

This is most likely to use the identifiers and descriptions for medication from a local or national patient care medicinal product dictionary, which will then require mapping to the PhV MPD.

- The expressed preference for a single national ADR reporting functionality rather than local or system specific functionalities. This would also allow clinicians to build familiarity with the system and the data, regardless of the setting in which they are working.

# 5 Results NCA survey

## 5.1 Overall survey results

Of the 23 NCAs that responded to the initial request to indicate whether initiatives for ADR reporting in clinical systems were in place in their countries, 11 of them responded positively (Table 1). 10 NCAs with initiatives for ADR reporting from clinical systems also responded to the follow-up questionnaire, while Denmark was lost to follow-up. The responses to the follow-up questionnaire collected are discussed in this section. Extensive information already provided following the initial request is also discussed in this section.

**Table 1: NCAs participating in survey**

| Round | NCA response received |
|---|---|
| Round 1:<br>Availability ADR reporting in clinical systems | AT, BE, BG, CZ, DE, DK, ES, FI, FR, HR, IE, IS, IT, LU, LV, NO, PL, PT, SE, SI, SK, NL, UK |
| Round 2:<br>Follow-questionnaire | BE, CZ, ES, HR, IS, NL, NO, PT, SE, SI, UK |

AT=Austria, BE=Belgium, BG=Bulgaria, CZ =Czech Republic, DE=Germany, DK=Denmark, ES=Spain, FR=France, HR=Croatia, IE=Ireland, IS=Iceland, IT=Italy, LU=Luxembourg, LV=Latvia, NO=Norway, PL=Poland, PT=Portugal, SE=Sweden, SI=Slovenia, SK=Slovakia, UK=United Kingdom

The NCAs reported initiatives with different levels of integration into the clinical systems (figure 4). These levels of integration vary from an incorporation of a link to the online ADR reporting webform of the NCA if a clinician wants to report an ADR (e.g. PT, IS and SE), to a fully integrated dataflow, which actually uses information from the clinical system (e.g. UK).

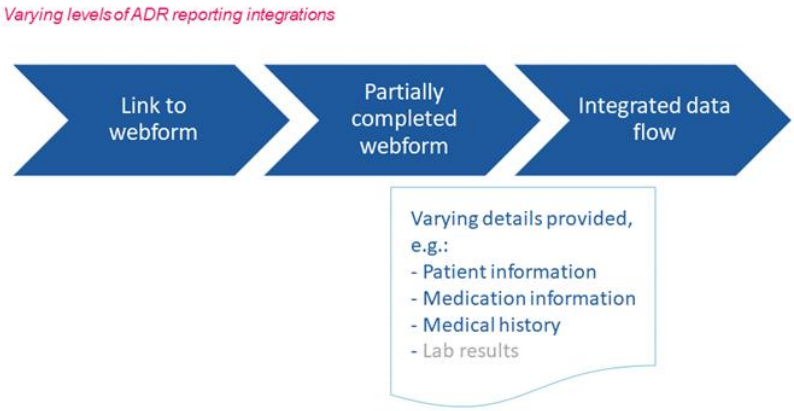



*Figure 4. Levels of integrated ADR reporting functionalities*

Two NCAs (NL and PT) described initiatives without an integration of the dataflow. These are considered out of scope of this working paper. Information on two initiatives that were halted in NL will be discussed separately (see section 5.3 Impact of initiative on ADR reporting and barriers for reporting). For the remaining eight countries, the responses to the follow-up survey (round 2) are discussed in this section.

Table 2 depicts the clinical systems utilized for ADR reporting and whether the system is in development or already in production at the NCAs.

**Table 2: Relevant clinical systems with ADR reporting functionalities for each country**

| Country | Clinical system with ADR reporting functionality in production | Clinical system with ADR reporting functionality in development |
|---|---|---|
| BE | GP | |
| ES | | GP and hospital |
| SI | GP and pharmacy | hospital |
| NO | Patients own digital health environment | |
| IS | GP and hospital | |
| HR | | GP, pharmacy and hospital |
| SE | | hospital |
| UK | GP, pharmacy, hospital and Risk Management System | Risk Management System |

Belgium, Iceland, Norway, Slovenia and United Kingdom have a system in production, while Croatia, Spain and Sweden only have systems in development. In addition, Slovenia and the United Kingdom are further developing ADR reporting functionalities within their clinical systems.

### Reporting functionalities mentioned in survey

ADR reporting functionalities are mostly operational in GP systems (BE, SI, IS and UK), with development activities ongoing for GP systems in two additional countries (ES, HR). Whereas ADR reporting functionalities in hospital systems are operational in only two countries (IS, UK), more development work is ongoing for hospital systems (ES, SI, HR, SE). For pharmacy systems, ADR reporting functionalities are operational in two countries (SI and UK), and development is ongoing in one country (HR).

Since answers to the detailed questions were generally the same for GP, pharmacy and hospital systems, the results are clustered by individual countries.

In general, there is variability on how drug information is provided for clinical systems. Drug information is provided at different levels and the level of integration of ADR reporting in clinical systems also varies.

## 5.2 Drug information provided by clinical systems

### 5.2.1 Patient care systems (GP, hospital and pharmacy)

#### Coding of suspect or concomitant medication

All countries report that the clinical systems provide coded suspect/concomitant medication for the ADR report (BE, ES, SI, IS, HR, UK, SE), in some countries further supplemented with free text (BE, ES, SE).

#### Level of precision of coding; suspect and concomitant medication

The level of precision of coding of the suspect and concomitant medication varies between countries and is illustrated in table 3. Of interest are the patient care systems of BE, ES and UK, since these systems provide the most explicit detail for the suspected drug (e.g. `amlodipine besylate 5 mg tablet`). The availability of this level of precision facilitates the selection of MPID/PhPID for the ICSRs.

**Table 3: Level of precision of coding suspect and concomitant medication**

| | Level of precision | | | | | | |
|---|---|---|---|---|---|---|---|
| **MS** | **Officially licensed medicinal product name** | **Brand** | **Batch Number** | **Substance** | **Level corresponding to** | | |
| | | | | | **Amlodipine besylate 5 mg tablet** | **Amlodipine 5 mg tablet** | **Amlodipine 5 mg** |
| BE | x | x | X (suspect medication only) | | X (suspect) | X (concomitant) | |
| ES | x | x | | x | x | | |
| IS | | x | | | | | x |
| HR | | | | | | x | |
| SE | x | | x | | x | x | |
| SI | x | x | x | | | x | |
| UK | | x | X (suspect medication only) | | x | | |

Usually there is the same approach for marking drugs as either suspect or concomitant. The most common approach is tagging the chosen suspect drug as ‘suspect’ and including all other current drugs as ‘concomitant’. An example of (de-)selecting medications in the Belgian integration is shown in figure 5.

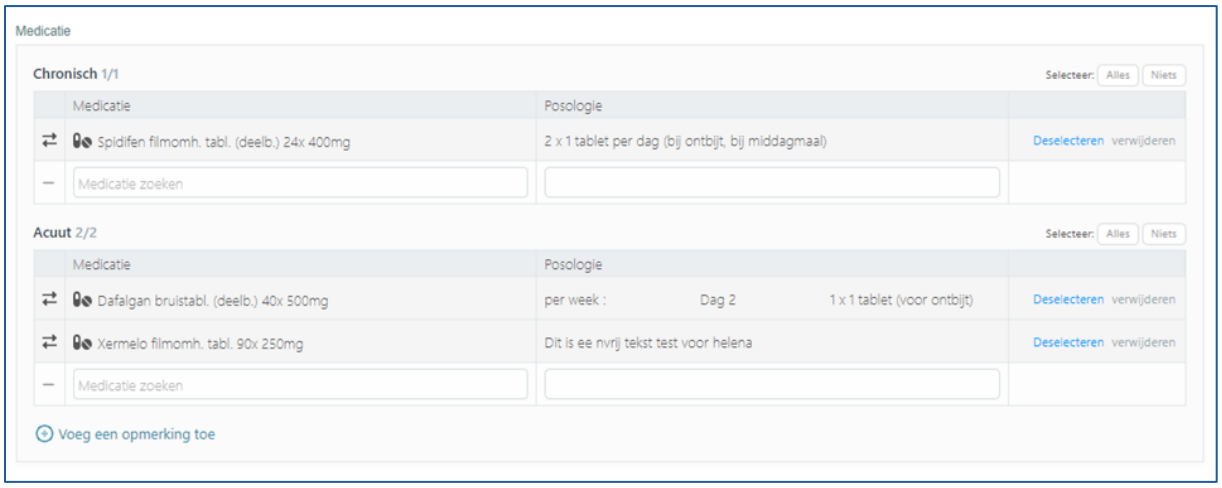



*Figure 5. Screenshot (de)selection of medications in an integrated ADR reporting functionality in Belgium.*

## Medicinal product diary used for coding, processing of medicinal product by NCA

The medicinal product dictionaries used for coding in the clinical systems as reported by the NCAs are included in table 4. This table also indicates how the medicinal product is processed by the NCA.

**Table 4: MPD used in clinical system and method of processing the medicinal product by NCA**

| MS | Based on NCA dictionary | Clinical care MPD | Clinical system's own MPD (commercial or local) | Automatic: use of same dictionary | Automatic: mapping available | Manual recoding required |
|---|---|---|---|---|---|---|
| BE | x | | | x | | |
| ES | x | | | x | x | |
| HR | x | | | | x | |
| IS | | x | | | | x |
| SE | | | x | | | x |
| SI | x | | | | | x |
| UK | | x | | | X (expansion of mapping in development) | |

## Batch number

Four countries (BE, SI, UK and SE) have indicated that batch numbers are collected in the clinical care systems.

### Barcode scanning

Barcode scanning could provide additional information on the products related to ADR reporting. Of the systems from which information was gathered with the follow-up questionnaire, only Croatia stated that barcode scanning provides additional information on the drug that is associated with the ADR.

However, the Croatian authorities noted that it is rarely used by general practitioners (as expected, since it is unlikely that prescribing systems store the barcode).

### Transmission of information on relevant past drug history

ES, IS and SE reported that their clinical systems do not transmit information on the relevant past drug history into the ADR report. In countries where these data are transmitted, there is variation between the type of data, as shown in table 5.

**Table 5: data on relevant past drug history transmitted in the ADR report.**

| MS | Coded drug information: Selection made by HCP | Coded drug information: All medication | Free text |
|---|---|---|---|
| BE | x | | |
| HR | x | | x |
| SI | | | x |
| UK | | x | |

## 5.2.2 Patients own digital health environment

Norway is the only country that mentioned to have a system for ADR reporting within the patient's own digital health environment. A personal digital healthcare environment is a place where medical information is kept for a patient: from health care providers, from the patient's own personal records and from apps that monitor health and exercise, for example. It is an online environment only accessible for patients. The information within this environment can be used for ADR reporting by the patient. For the Norway system, suspect and concomitant medication is coded with the national MPD based on the NCAs regulatory dictionary.

Coding is provided for officially licensed product name, brand, substance, level corresponding to `amlodipine 5 mg tablet' and the batch number for suspect drug only if manually provided.

The medication is marked as suspect or concomitant by asking separate questions, since directly importing is not possible due to legal issues. Furthermore, relevant past drug history is not transmitted automatically, and needs to be provided manually by the patient. The PhV ADR database and clinical system use the same drug dictionary, but there is manual coding and re-coding necessary by the NCA.

### 5.2.3 Risk Management Systems

PT and UK both indicated to have ADR reporting available within a RMS employed in health care organisations.

RMS is the software system that manages the organisation's risk management, providing facilities for staff to enter, track, report and learn from safety events (including near misses). Medication safety events (e.g. missed administrations, accidental overdose, wrong medication administered) are captured in such a system to evaluate the risk and to make improvements in care following its evaluation. This information can also be relevant for ADR reporting (e.g. anaphylaxis due to penicillin administered to a known penicillin-allergic patient).

UK has the integration of ADR reporting in the RMS in development, but UK reported that coding and other specifications of the ADR reporting functionality do not differ from the GP, hospital and pharmacy systems. PT reported a system in place, but this system is deemed out of scope, since it includes no integration from the clinical and PhV system. This system will be discussed in recommendation 7.5.

## 5.3 Recording the suspected ADRs and triggers to send an ADR report

The NCAs were requested to indicate how the suspected ADR is recorded in the clinical system. No clear pattern could be established from these answers; the suspected ADRs were recorded in different fields (table 6). No differences were found between clinical systems from the same country.

**Table 6: System field used for recording suspected ADRs**

| MS | Field | GP | Hospital | Pharmacy | Patient's own health environment | Risk Management System |
|---|---|---|---|---|---|---|
| BE | Intolerance section | x | | | | |
| ES | (1) Reason for stopping medication<br>(2) Dedicated field in patient record | x<br>x | x<br>x | | | |
| UK | Dedicated field in patient record | x | x | x | | x |
| IS | Dedicated field in ADR reporting form | x | x | | | |
| SE | Dedicated field in ADR reporting form | | x | | | |
| NO | Dedicated field in ADR reporting form | | | | x | |
| SI | No dedicated field | x | x | x | | |
| HR | No dedicated field | x | x | x | | |

Where the ADR is captured in the patient record, this does not automatically lead to triggering an ADR report to the PhV Centre. Most NCAs (BE, ES, UK, IS, SE, SI, HR, NO, PT) reported that the HCP/patient is the trigger to send an ADR report to the NCA.

In addition, UK reported that a prompt is triggered to suggest that an ADR report (i.e. Yellow Card) can be sent to the NCA when a drug is stopped or a drug sensitivity is recorded in the electronic health record. This prompt can be discarded or postponed.

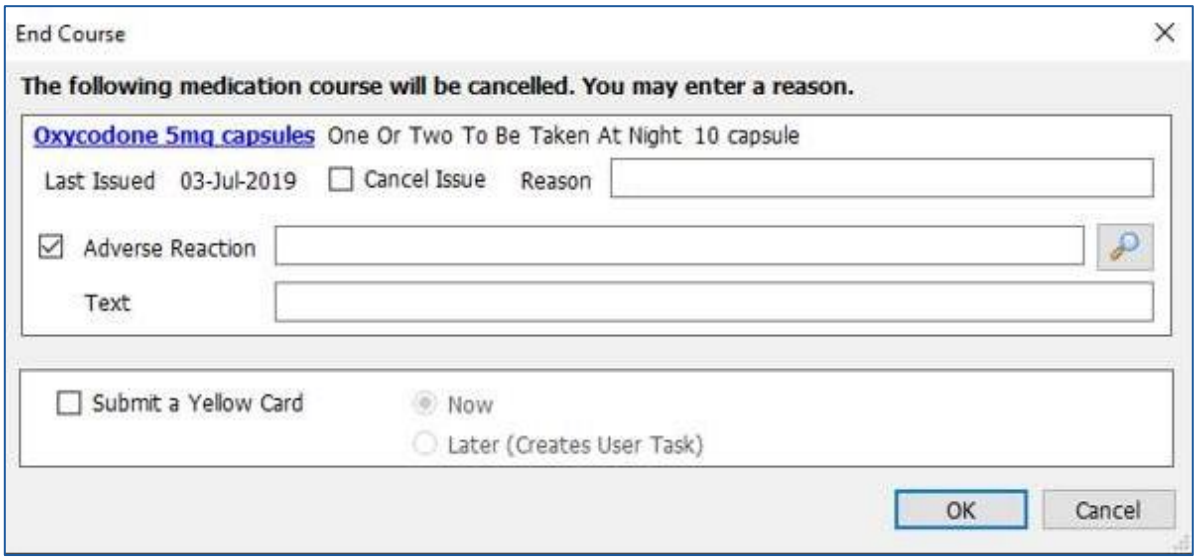



*Figure 6. Example of recording ADR as reason for stopping medication in UK EMIS system*

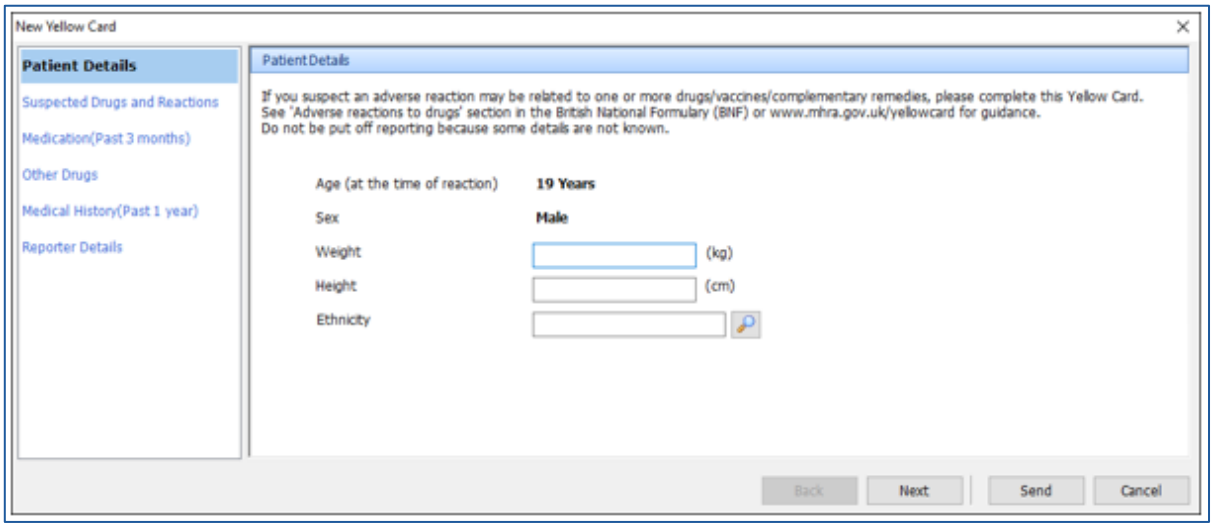



*Figure 7. Example of integration of a trigger for ADR reporting in clinical system in the UK EMIS system*

## 5.4 Impact on ADR reporting rates and barriers for reporting

The NCAs were requested to provide 1) the year of availability of the ADR reporting functionality in the clinical systems and 2) information on the success of this functionality in terms of percentage of cases received through these clinical systems and changes in patterns. The results are provided in table 7.

**Table 7: Impact of initiative on ADR reporting**

| MS | Year of availability | Percentage of cases received annually | Change in pattern |
|---|---|---|---|
| BE | 2021 | 10% of HCP cases | No |
| SI | 2018 (GP)<br>2019 (Pharmacy) | 2% of cases | Monthly instead of a maximum of 5 reports per year |
| IS | 2014 | Less than 10% | Not reported |
| UK | Became available in different systems from 2010 and later | 40% (~7000 cases) | Large increase |
| SE | 2021 | 17-18% of the reports of 1 region that has an initiative in place | Not reported |

The success of these initiatives varies. Although some countries report promising percentages of cases received, this does not necessarily lead to a substantial change in ADR reporting pattern. The implementation in the UK appears most successful and will be further discussed as a best practice in section 7.2.

The following behavioural barriers hampering ADR reporting in the current clinical care systems were mentioned by the NCAs: 1) lack of awareness of the ADR reporting functionality (IS), 2) accessibility within the clinical system (UK), 3) lack of triggers to warn for an ADR in the clinical system (UK), 4) lack of support to attach MRI/CT results, and 5) lack of time (ES).

The following barriers hampering integration of ADR reporting in the current clinical care systems were mentioned by the NCAs:

- No national phase and/or multiple suppliers or different systems (SI, UK, NO, SE);
- Costs/funding (SE, NO, NL, UK);
- Privacy aspects (NL);
- Interaction problems due to changes in both the clinical systems and PhV center system (NL);
- Incentives and political aspects of HCPs/organizations (HR, NO);
- Lack of standardization of data in clinical systems (ADRs and drug information) (PT, NL).

NL referred to a qualitative study on the barriers for registering ADRs in EHRs (Geeven, 2022) and mentioned that two initiatives were discontinued due to privacy aspects, costs and interaction problems.

These discontinued initiatives are discussed in the grey box below. Strictly speaking, the NL initiative with ADRs from the Inflammatory Bowel Disease (IBD) registry is not part of the spontaneous reporting system. However, a general lesson can be learnt from the Dutch initiatives, that having technical solutions in place to facilitate ADR reporting is not necessarily a guarantee for continued success.

**Two Dutch initiatives**

The Netherlands had two relevant initiatives which were halted due to various reasons.

1. Facilitated spontaneous reporting of ADRs via GP systems

ADR reporting was facilitated via a GP Clinical Decision Support System that is used by 30% of Dutch GPs. Once a GP enters an ADR in the patient record, an alert pops up to encourage the reporting of the ADR. This then opens a partly completed reporting form within the GPs IT system for further completion and sending to the National Pharmacovigilance Centre (Lareb). Integrating the reporting form in the GP system in a logical, acceptable way without asking too much or too little extra information, while ensuring the privacy of the patient was challenging. Drug information was mostly provided at substance level (with strength and dose form being available in separate data-elements). The number of ADR reports received via this mechanism was low.

2. Automatic sending of reported ADRs that are recorded in the IBDREAM (also DREAM-RA and SpA-net registries).

IBDREAM registry is a multicentre registry that prospectively collects medical data, including ADRs, from Inflammatory Bowel Disease (IBD) patients in daily practice in five hospitals in The Netherlands. Enrolled patients receive a personal and secure account within the IBDREAM registry, allowing them to inform their HCP about ADRs. Within IBDREAM, patients can select one of the used drugs according to the National Drug Dictionary used (Z-index) and report ADRs (open text field) related to this specific drug. Drug information can be provided at generic substance level (or combination of substances), as well as with brand name. These ADRs are verified by the HCP and recorded in the IBDREAM registry. In addition, ADRs can be recorded by the HCP. Thus, both patients and HCPs may report ADRs, while all ADRs were verified and registered by HCPs. ADRs that are registered in IBDREAM are directly electronically forwarded to the Netherlands Pharmacovigilance Centre (Lareb). Fine-tuning the information received from the registry into the spontaneous reporting database was a challenge. Both initiatives used Application Program Interface (API) for authorized organizations to transmit ADR reports that are subsequently imported to the PhV database of Lareb. Lareb's Web API also had the ability to lead an end user to a form where data can be completed. If organisations cannot use the Web API, for example due to infrastructural limitations, data can be uploaded in a CSV format. Each stakeholder pays for its own maintenance costs. Complexities related to ensuring the privacy of the patient and regular maintenance because of multiple system changes (either at the PhV Centre and/or the exchanging system(s)) ultimately led to decision to no longer continue these initiatives.

# 6 Transforming drug information from clinical systems into IDMP descriptions for ICSRs and special situations to consider

## 6.1 Applying working paper 8.7 guidance to drug verbatims transmitted by clinical systems

The NCA survey shows that medications can be transmitted from clinical systems as drug verbatims with varying levels of precision. The illustration in figure 8 below shows how the use of NHS dm+d or Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) medicinal product terminologies offer medicine descriptions at different “levels of abstraction” which can then be used to record an adverse reaction, allergy or intolerance to a therapeutic substance (in this example, paracetamol) in an EHR, and which may then be sent onward in an ADR report. (NHS England, 2017):

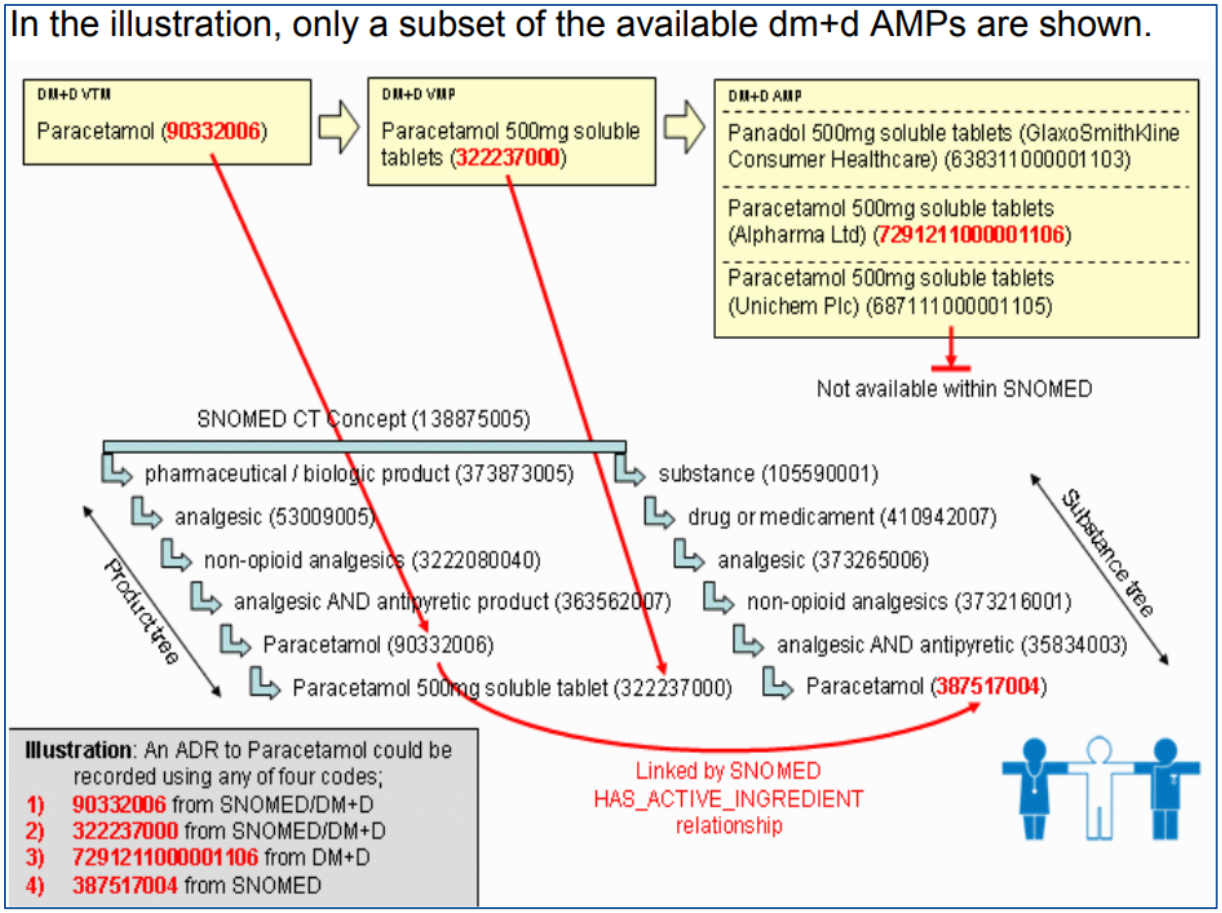



*Figure 8. Visualisation of using dm+d or SNOMED CT codes for recording an adverse reaction, allergy or intolerance to paracetamol in the UK NHS*

The level of precision of a suspected or concomitant medicinal product may depend on technical specifications issued by NCAs (e.g. Danish medicines authority DKMA has published detailed specifications for ADR reporting from GP systems (DKMA, 2017)), or on agreements made between NCAs and clinical system developers. The type of medicinal product as well as similar medicines being available nationally can also be factors affecting the level of precision. For biologicals for example, recording of the brand name may occur when a biosimilar is available whereas only a non-proprietary name is recorded if no biosimilar is on the market (Klein, 2019). Furthermore, the level of precision may depend on the trigger for sending the ADR report.

An allergy/intolerance is more likely to be recorded at substance level than at MPID level. When stopping medication because of a suspected ADR is the trigger for an ADR report, a more precise drug level would be appropriate. The UK screenshot in figure 6 shows that ‘oxycodone 5mg capsules’ is discontinued because of a suspected ADR.

UNICOM Working paper 8.7 describes various levels of drug verbatims and how to transform these into IDMP identifiers for the ICSR. In this section we will apply the guidance from D8.7 to drug verbatims as potentially transmitted by clinical systems. A high-level summary of D8.7 guidance is provided in figure 9.

As a first step, it is important to check the drug verbatim for confusing drug information. The NCA answers show that although drug verbatims are often transmitted to them as a standardised MPD terms, this is sometimes supplemented with free text. In some countries free text is used for transmitting ‘relevant past drug therapy’ from the clinical system. In the situation where ADRs are received via clinical systems and free text is transmitted, it is important to be aware of acronyms, abbreviations and synonyms used in clinical practice. When drug allergies are the trigger for ADR reporting, one should be aware that these may be recorded as therapeutic classes (e.g. clinical systems may document drug allergies as therapeutic class, e.g. ‘penicillins’ or ‘betalactams’ instead of ‘amoxicillin’). However, therapeutic classes cannot be reflected in the Drug Section(s) of the ICSR: when only the therapeutic class is available, this information should be reflected in the case narrative (EMA, 2017).

As a second step, UNICOM Working paper 8.7 describes that by taking reliable contextual information into account, an ‘imputed level of drug information’ can be achieved, which leads to a more precise selection of MPID or PhPID in the ICSR, as well as more details in the name part data elements. This is particularly relevant when the level of precision is lower than MPID. The ‘imputed drug information’ does not have a dedicated data element in the ICSR but is only a conceptual step for establishing the most precise level of drug information.

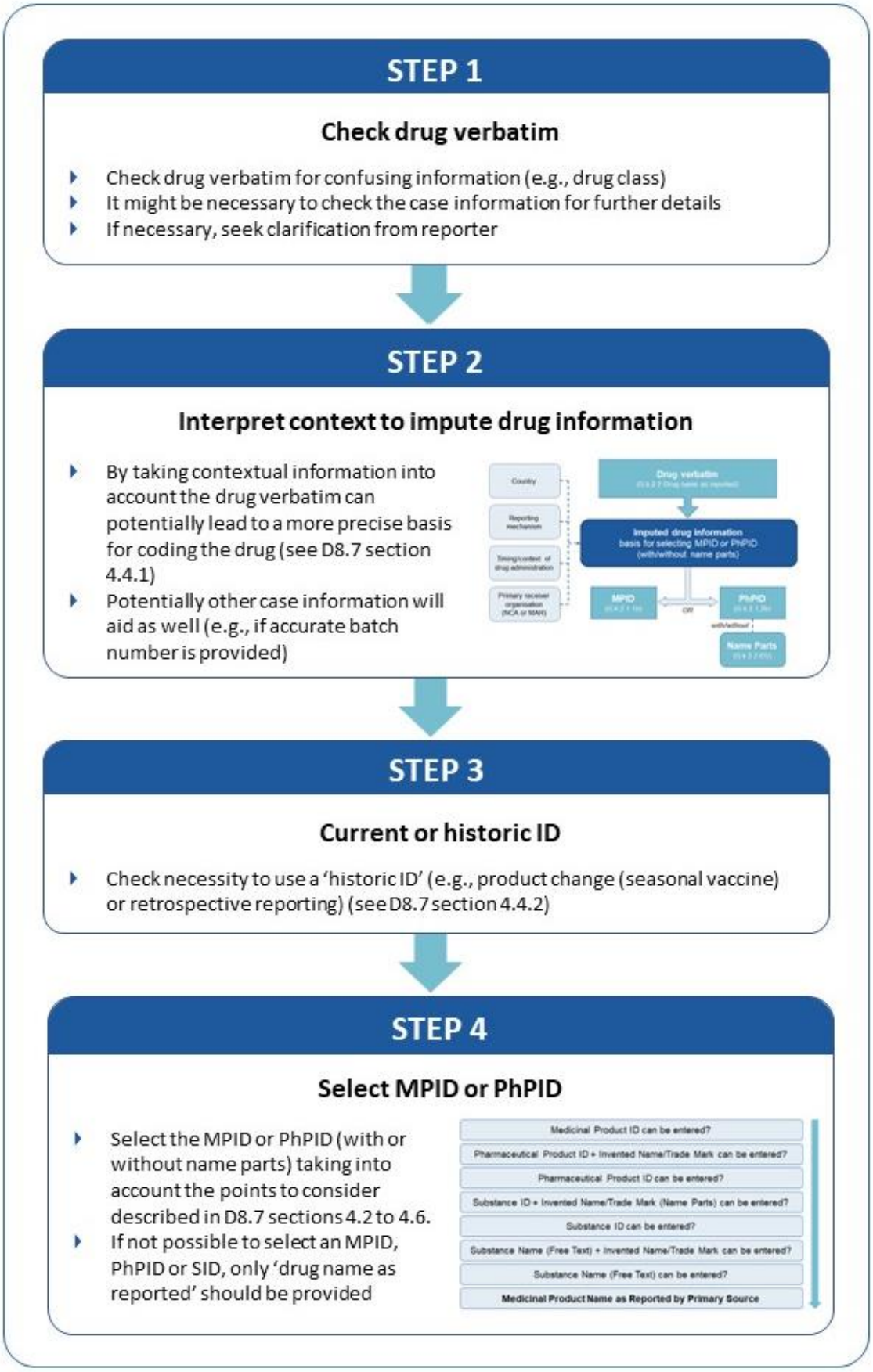



*Figure 9. High level summary of IDMP coding principles and guidance*

In the situation where ADRs are received via clinical systems, three contextual aspects are already known: (1) the primary receiver being the NCA or (regional) PhV centre, (2) the country and (3) the reporting mechanism (a clinical system). The 4th aspect (timing and context of drug administration) can be useful in specific situations when more information is available 'in the background', as illustrated by the following examples:

**Example:**

Country A has received a report of a suspected ADR associated with a COVID-vaccine. The report does not specify the name of the vaccine. At the time of vaccination, the only COVID vaccine available in Country A was Comirnaty (Pfizer) mRNA vaccine. By using this background knowledge, a PhPID Level 4 could be imputed. As long as only 1 MPID would be available for the Comirnaty (Pfizer) mRNA vaccine, even the MPID could be imputed. Without using contextual information, based on only 'COVID vaccine' as drug verbatim it would not even be possible to code PhPID level 1.

**Example:**

In December 2019 a patient receives the yearly flu vaccine and experiences fever. In the clinical record the vaccine is captured as 'seasonal flu vaccine'. For a seasonal influenza vaccine, the strains can change with the season. This implies that a new MPID shall be assigned for the vaccine each time the strains are changed. Using contextual information such as the date of administration of the vaccine (timing of drug administration) and knowledge on the specific vaccines used in the vaccination programme (context of the drug administration), it is possible to select an MPID even though the suspected vaccine is recorded in non-specific terms.

We have applied this concept of 'imputed drug information' on 3 drug verbatims as potentially received from clinical systems in different countries.

### Example 1

The Croatian authorities (HALMED) receive an ADR via a GP system with the drug verbatim 'amlodipine 5mg tablet'

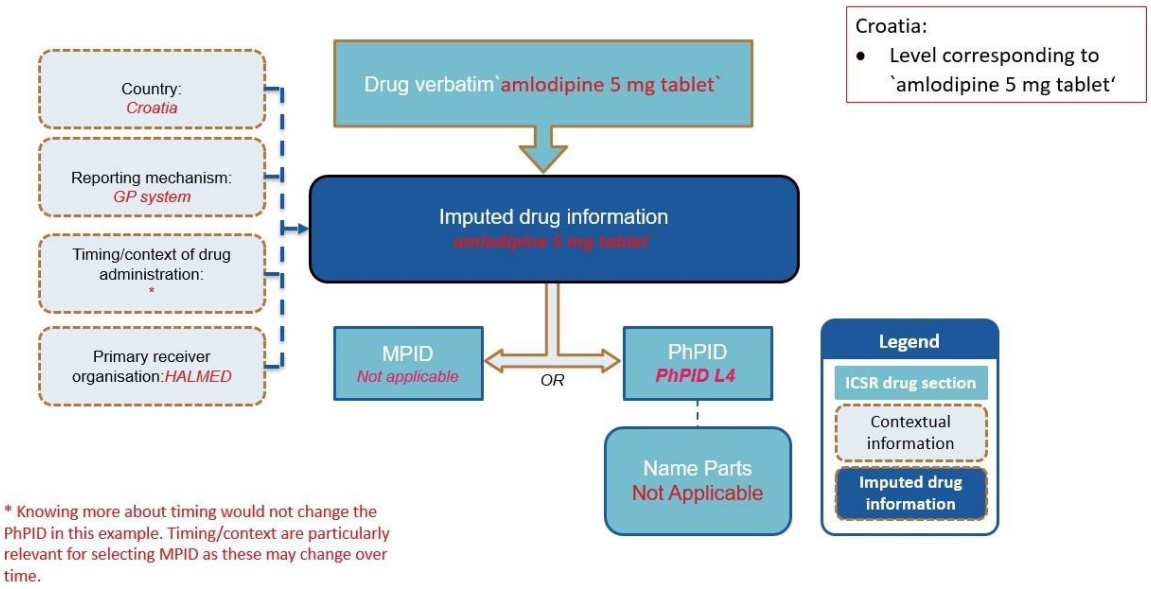



*Figure 10. Flow chart of using Imputed Drug Information to select MPID/PhPID/name parts for precise drug coding based on Croatian example*

In this example the drug verbatim received from the clinical system is ‘amlodipine 5mg tablet’. Based on this information only a PhPID L4 for ‘amlodipine 5mg tablet’ can be selected. With several ‘amlodipine 5mg tablets’ being available on the Croatian market, it is not possible to select a more precise identifier or assign name parts.

## Example 2

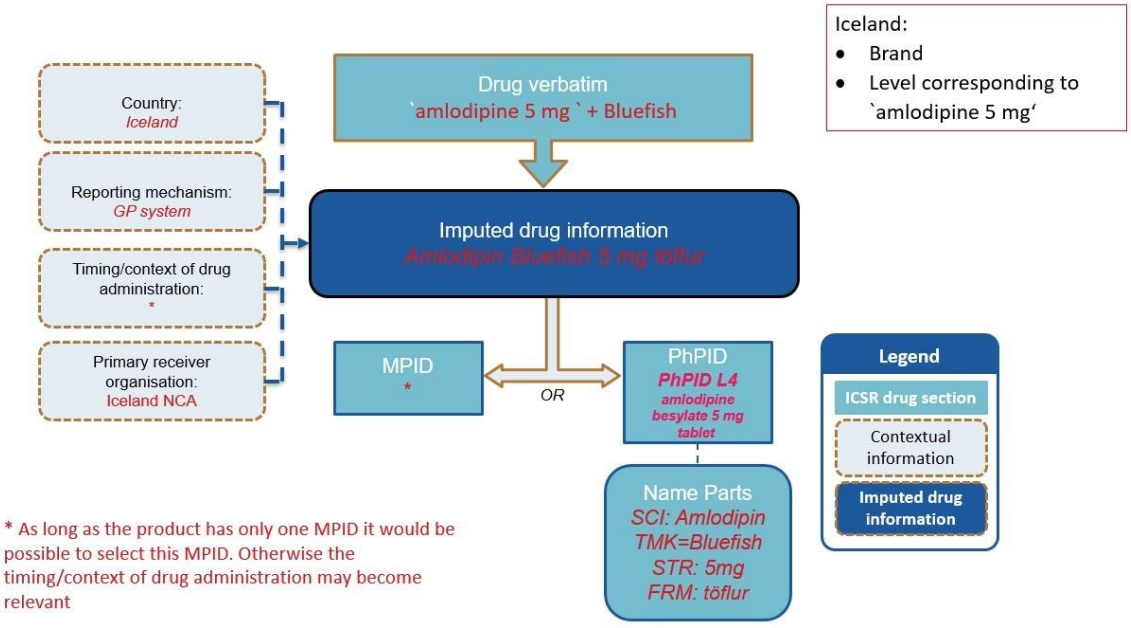



*Figure 11. Flow chart of using Imputed Drug Information to select MPID/PhPID/name parts for precise drug coding based on Icelandic example*

In this Icelandic example, the drug verbatim received from the clinical system is ‘amlodipine 5mg Bluefish’. In Iceland there is only one marketing authorisation for ‘amlodipine 5 mg’ in combination with trademark ‘Bluefish’: Amlodipin Bluefish 5mg töflur. For Bluefish amlodipine, only ‘tablets’ are licensed (5mg as well as 10mg); for both its composition is stated as ‘amlodipine besylate’.

Using this ‘imputed drug information‘ it is possible to capture more precise details in the ICSR:

- Since it is known that the dose form is ‘tablet’, and the product contains amlodipine besylate, PhPID L4 can be captured as ‘amlodipine besylate 5mg tablet’ (instead of ‘amlodipine 5mg’ as verbatim).

- It is also possible to provide more name part data elements (not just ‘Bluefish’ as verbatim).

- As long as the product would have only one MPID it would even be possible to select this level.

## Example 3

A regional PhV centre in Spain receives an ADR via a clinical system, with the drug verbatim stating the officially licensed product name (Norvas 5mg comprimidos), as well as a PhPID L4 (amlodipine besylate 5mg tablet):

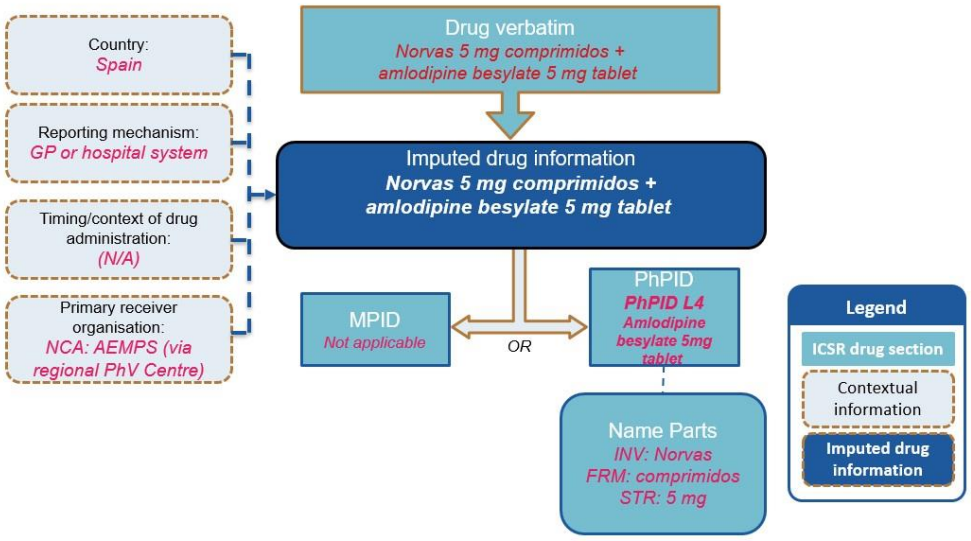



*Figure 12. Flow chart of using Imputed Drug Information to select MPID/PhPID/name parts for precise drug coding based on Spanish example*

In the Spanish example the officially licensed product name ‘Norvas 5mg comprimidos‘ is provided together with a PhPID L4 reflecting the salt and dose form. For the purpose of this example, it is assumed that the product has more than 1 MPID. The ‘imputed drug information’ does not lead to more precision. The Drug Section in the ICSR will be populated with a PhPID L4 for amlodipine besylate 5mg tablet‘ as well as applicable name parts.

The third step is to decide whether a historic IDMP identifier is required. This is particularly relevant when suspected ADRs associated with drugs that have been taken a long time ago are reported

retrospectively (e.g. due to media attention). Historic identifiers can also be relevant for populating ICSR data elements 'Relevant Past Drug History' and 'Relevant Past Drug History of Parent'. NCA answers show that information on relevant past drug history is systematically transmitted in each country and that there is variability on the format: as free text, or as a standardised term from a clinical MPD. Specific attention should be paid to products for which the composition will change seasonally, as illustrated by the example of the seasonal flu vaccine.

The fourth and last step is to assign the MPID or PhPID (with or without name parts), following the decision flow from the EU ICSR Implementation guide (see Appendix for a short summary). According to this guide, 'product name parts should be used if the MPID cannot be selected and if the medicinal product has been reported as a brand/invented name'. The examples for step 2 show that the 'imputed drug information' can be used to assess which name parts can be populated.

In this section we have explored how to apply the guidance from D8.7 to drug verbatims transmitted from clinical systems. Overall, the same principles can be followed for transforming these drug verbatims into IDMP identifiers as for drug verbatims received via more traditional reporting mechanisms. The step to achieve an 'imputed level of drug information' is still relevant for verbatims transmitted from clinical systems, even though 3 out of 4 contextual aspects are already known. Examples illustrated that this conceptual step can lead to more precise drug information in the ICSR, and that name part data elements. It is important to be aware that therapeutic classes cannot be processed in the ICSR Drug Sections. This can be especially relevant when the trigger for ADR report is the recording of an allergy/intolerance.

## 6.2 Special situations

Since information in clinical systems is collected primarily to manage the patient and for administrative purposes, it does not necessarily meet the needs for PhV reporting in every situation. The information recorded in ICSRs is focused on performing a causality assessment whether a medical event in a patient is likely to be causally related to the use of a medicine (Norén, 2010). As a consequence, whereas health records are expected to provide complete patient health histories and medication profiles in an accessible and centralized manner, the record may not contain the information required in the ICSR, or information in the EHR is structured differently.

With these differences in mind, four special situations are highlighted where ADR reports received from clinical systems need careful attention when entering in PhV databases to ensure that the ICSR Drug Section will be populated correctly:

1. 'parent-child report' (parental exposure);
2. drug interactions;
3. medication error;
4. excipients.

'Route of administration' has been defined by EDQM as the 'path by which the pharmaceutical product is taken into or makes contact with the body, for example intravenous use, oral use, ocular use, oromucosal use'. A drug verbatim may seem to reflect the route of administration, for example when this is part of the official medicinal product name as licensed and shown on the package. However, the route of administration is not part of the PhPID generation. When receiving a drug verbatim with a route of administration, this can be ignored for selecting the PhPID.

It should be noted that the actual path through which the patient received the medicine may be different from the authorised route of administration. For example, when there is a need for parenteral administration or when a medication error has occurred.

### 6.2.1 Parent-child reports (parental exposure)

A special situation to consider is when a child/foetus has been exposed to a medicine via maternal/paternal exposure and experiences a suspected ADR. Information on both the parent and the child/foetus should be provided in the same ICSR, referred to as a parent-child/foetus report. The ICSR section for the patient will contain only information for the child/foetus. The ICSR has a dedicated section where characteristics concerning the mother or father, whoever was the source of exposure to the suspect medicinal product, should be captured (EMA, 2017). The example illustrates the importance of acknowledging the difference between structured information in the ICSR and how information is captured in clinical records.

**Example:**

A health care professional wants to submit a report about a breast-feeding infant who experienced slightly elevated TSH (thyroid stimulating hormone) after being exposed to lithium through the mother. The patient record for the mother will state that the mother used '3 tablets of 400mg lithium daily'. Since the infant did not receive the medication directly (but was exposed via the mother) there is probably no medication record for lithium in the infant's patient file.

The pharmacovigilance centre needs to create a 'parent-child' report. Since the infant experienced the ADR, the 'patient' section is populated with information on the infant. Based on the drug verbatim ('3 tablets of 400mg lithium daily') a PhPID L4 for lithium 400mg tablets should be selected as suspected medication. The route of administration (G.k.4.r.10.) for the infant who experienced the ADR is 'transmammary'. Details for the mother can be captured in the 'parent section' of the ICSR. The route of administration for the mother ('oral') should be captured in data element Parent Route of Administration (G.k.4.r.11) .

### 6.2.2 Interactions

For reports describing drug interactions, which concern drug/drug or interactions with other non-drug compounds (e.g. food, device, alcohol, etc), the ICSR data element G.k.1 ‘Characterisation of Drug Role’ should be completed with the value ‘3’ (= ‘interacting’).

**Example:**

When a case describes an interaction between 2 drugs the ICSR Data element G.k.1 ‘Characterisation of Drug Role’ is to be completed with the value ‘3’ (=interacting) for all suspected interacting medicines.

If an interaction is suspected with food or other non-drug compounds, ICSR Data element G.k.1 ‘Characterisation of Drug Role’ should be populated with ‘3’=interacting’ for the suspect drug (for evaluation purposes, all interacting drugs are considered to be suspect drugs). The information concerning the interacting food or other non-drug compounds should be provided in the case narrative. The type of interaction (e.g. drug interaction, food interaction, alcohol interaction, etc.), should be also captured in Section E.i Reaction(s) / Event(s) along with any event(s) resulting from the suspected interaction.

A screenshot of a Danish example of an ADR reporting functionality integrated in a GP system, taking into account an interaction between Budovar and Prednisolon is shown in figure 13.

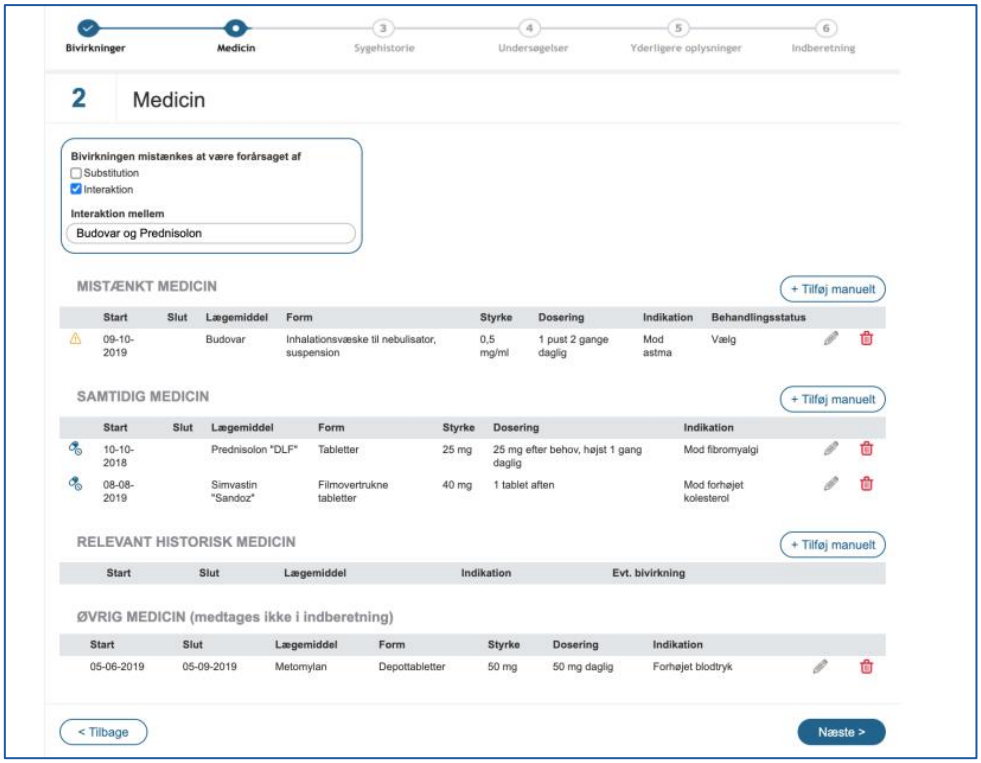



*Figure 13. Screenshot of medication information with ‘drug interaction’ in Danish GP ADR reporting functionality*

### 6.2.3 Medication error

In 2015, the EMA has published a good practice guidance to clarify specific aspects related to recording, coding, reporting and assessment of medication errors in the context of EU PhV activities (EMA, 2015). Here it is detailed that for medication errors where the patient did not receive the actual prescribed medicinal product but another medicinal product, repeatable Drug 'Sections G' should be completed with the information about the prescribed drug (selecting the characterisation of drug role as 'drug not administered'(value '4'), as well as the information on the dispensed drug as the 'suspect' drug (value '2).

**Example:**

An infant with nephropathic cystinosis was given mercaptopurine instead of mercaptamine. After taking the wrong medicinal product for 1 month, the infant developed pancytopenia but made a full recovery after the error was noticed and rectified. Whereas the clinical system may reflect that the ADR occurred due to mercaptopurine, it is important to provide both medications in the ICSR. In this situation, the repeatable ICSR Drug Section should be completed as follows:

The first iteration of Drug Section G.k should provide:

- G.k.1 'Characterisation of Drug Role' should be populated with '1'=suspect'
- G.k.2.2 Medicinal Product Name as Reported by the Primary Source: 'mercaptopurine'
- PhPID L1 for mercaptopurine
- Name parts: not applicable

The second iteration of Drug Section G.k. should provide:

- G.k.1 'Characterisation of Drug Role' should be populated with '4'=drug not administered'
- G.k.2.2 Medicinal Product Name as Reported by the Primary Source: 'mercaptamine'
- PhID L1 for mercaptamine
- Name parts: not applicable

### 6.2.4 Excipients

The EU legislation [DIR Art 1(3b)] defines 'excipient' as 'any constituent of a medicinal product other than the active substance and the packaging material', for example colouring matter, preservatives, adjuvant, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances.

Adverse reactions can occur with the excipients, for example allergies, lactose intolerance or effects of sugar in diabetic patients. GVP Module VI provides guidance for the situation where it is suspected that one of the excipients of the suspected medicinal product has caused the ADR.

In this situation, the ICSR Drug Section G.k. ‘Drug(s) Information’ should be repeated:

- One entry for the information on the suspected medicinal product
- A separate entry specifying the suspected excipient. The (Specified) SID for the excipient should be used if available, otherwise free text should be used. This suspicion of an ADR with the excipient should also be specified in the ICSR case narrative. GVP Module VI further recommends that if available, tests results (positive or negative) in relation to the causal role of the suspected excipient should be included in the ICSR Section F.r ‘Results of tests and procedures relevant to the investigation of the patient’.

**Example:**

When receiving a case of an allergic reaction to tartrazine as an excipient in ‘Claritromycine ratiopharm 250 mg, filmomhulde tabletten' the Drug Section in the ICSR should be repeated and populated as follows:

The first iteration of Drug Section G.k should provide:

- G.k.1 ‘Characterisation of Drug Role’ should be populated with ‘1’=suspect’
- G.k.2.2 Medicinal Product Name as Reported by the Primary Source: ‘Tartrazine excipient of Claritromycine ratiopharm 250 mg, filmomhulde tabletten’
- PhPID L4 for clarithromycine 250mg filmcoated tablet (if coding MPID is not possible)
- Name parts: SCI = Claritromycine; TMK = ratiopharm; STR = 250 mg; FRM = filmomhulde tabletten

The second iteration of Drug Section G.k. should provide:

- G.k.1 ‘Characterisation of Drug Role’ should be populated with ‘1’=suspect’
- G.k.2.2 Medicinal Product Name as Reported by the Primary Source: ‘Tartrazine excipient of Claritromycine ratiopharm 250 mg, filmomhulde tabletten’
- Data element G.k.2.3.r.b can be used if the (Specified) Substance ID for the excipient is available, otherwise 'tartrazine’ can be provided as free text in data element G.k.2.3.r.1 Substance/Specified Substance name.

## 6.3 Impact of IDMP on NCA/PhV centre responsibility for coding precise drug information in the ICSR

Currently, exchange of drug information in the ICSR relies on a free text data element 'Medicinal Product Name as Reported by the Primary Source' (E2B(R3) G.k.2.2). In practice, this free text data element is often populated with a standardised term from the drug dictionary that is used in the PhV system. In today's situation, a mapping between the MPD used in clinical care and the dictionary used in the PhV database (as some NCAs have in place, see section 5.1) supports efficient processing. When no such mapping exists, a lot of manual coding/re-coding is required. A best practice for such mapping is shown by the UK MHRA.

The IDMP implementation status can vary between countries, but also between domains (regulatory versus clinical). It is possible that use of IDMP identifiers (MPID, PhPID or SID) will become mandatory in the ICSRs at some point in time in the future, but the implementation of IDMP in clinical systems is not yet mature or not even planned in every country. For ADR reporting from clinical systems and subsequent ICSR processing by NCA/PhV centres different scenarios will be possible:

A. IDMP identifiers can be transmitted from the clinical system

For the exchange of ADRs from clinical systems to the NCA/PhV centre there will be clear efficiency gains if the MPID can be provided by the clinical system, as this is the most precise IDMP level available in the ICSR. However, when less precise IDMP drug information is received from the clinical system, additional steps may be needed to establish the 'imputed drug information' and subsequent selection of the most precise IDMP identifier. Processing of drug information in the ICSR should ensure that also name part data elements are populated as appropriate.

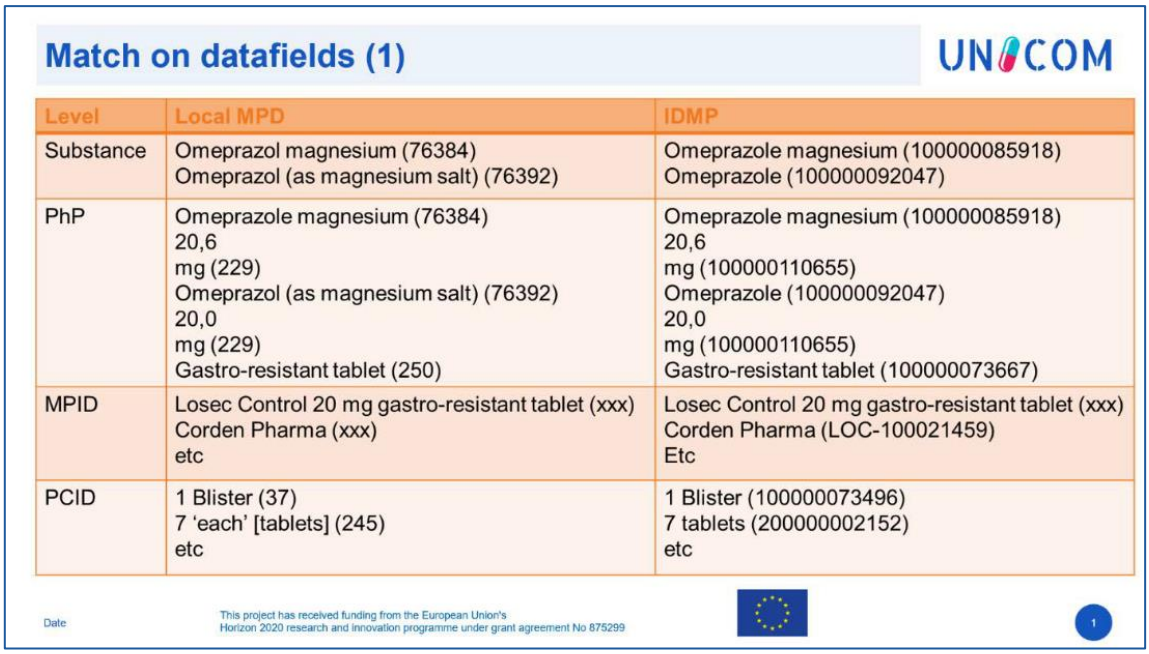
B. No IDMP identifiers can be transmitted from the clinical system

As in current practice, the ADR report will contain a text name, which is treated as the drug verbatim. The most appropriate IDMP identifiers and name part data elements can be selected following guidance developed in Working paper D8.7.

Selecting MPID/PhPID (with or without name parts) based on 'imputed drug information' may be associated with more work for the PhV centre compared to the current situation. Where PhV centres are already used to having a mapping in place between the MPD used in clinical care and dictionary used in the PhV database (or when systems use the same dictionary), it is recommended to take into account a certain level of automation of processing name part data elements in the ICSR and not only focus on the IDMP identifiers.

UNICOM Working paper 9.2 described an IDMP mapping strategy based on mapping only IDMP data elements relevant to product identification, such as mapping the PhPID, MPID, PCID to the corresponding IDs in the MPD. This was considered to be the most efficient solution the moment an MPD is already existing and is using its individual controlled vocabularies and product structure. This form will also help in keeping the mapping updated according to the terminologies evolving.

When there is a need to do a mapping between IDMP and an MPD for the purpose of ADR reporting and ICSR processing, it is recommended to use this strategy while also considering name part data elements.



**Match on datafields (1)**

| Level | Local MPD | IDMP |
|---|---|---|
| Substance | Omeprazol magnesium (76384)<br>Omeprazol (as magnesium salt) (76392) | Omeprazole magnesium (100000085918)<br>Omeprazole (100000092047) |
| PhP | Omeprazole magnesium (76384)<br>20,6<br>mg (229)<br>Omeprazol (as magnesium salt) (76392)<br>20,0<br>mg (229)<br>Gastro-resistant tablet (250) | Omeprazole magnesium (100000085918)<br>20,6<br>mg (100000110655)<br>Omeprazole (100000092047)<br>20,0<br>mg (100000110655)<br>Gastro-resistant tablet (100000073667) |
| MPID | Losec Control 20 mg gastro-resistant tablet (xxx)<br>Corden Pharma (xxx)<br>etc | Losec Control 20 mg gastro-resistant tablet (xxx)<br>Corden Pharma (LOC-100021459)<br>Etc |
| PCID | 1 Blister (37)<br>7 'each' [tablets] (245)<br>etc | 1 Blister (100000073496)<br>7 tablets (200000002152)<br>etc |



*Figure 14. Example mapping IDMP identifiers (Unicom Community of Expertise, 25-02-2022 Leonora Grandia, Z-Index)*

For MPDs based on SNOMED CT, there is documentation available describing the compatibility with IDMP. See: http://confluence.ihtsdotools.org/download/attachments/115870807/1b.%20SNOMED%20CT%20Drug%20Model%20for%20supporting%20National%20Extension%20V1.0.pdf?api=v2)

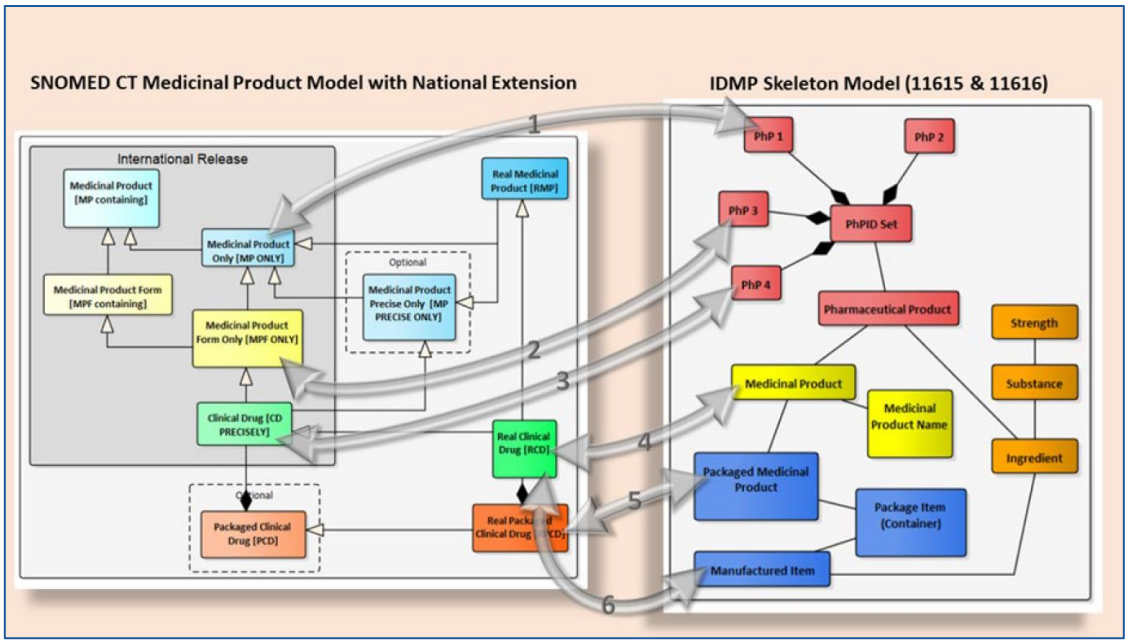



*Figure 15. SNOMED CT Product Model relation to IDMP Skeleton Model*

**Best practice for mapping clinical and regulatory drug dictionary in UK**

NHS dm+d is the NHS dictionary of medicines and devices used in clinical systems. The UK NCA (MHRA) has its own drugs dictionary. The MHRA was expecting to receive increasing volumes of ADR reports from clinical systems, and in these reports the drugs may be identified using the names from three levels of the dm+d dictionary. The dm+d drug concepts are however not compatible with MHRA drugs dictionary terms and would require manual population of the drug terms. The MHRA has therefore undertaken a process to build up a mapping between dm+d concepts and MHRA drugs dictionary terms for Yellow Cards received from clinical systems. These mappings are for MHRA internal use only.

A mapping of over 135,000 medicinal terms from the dm+d dictionary to the MHRA's Drugs Dictionary was created to enable automatic processing of these reports and standardise coding practices. As the MHRA drugs dictionary is unique there were no specific guidelines in place. A set of principles were drafted and data validated internally. Once these initial stages were completed an internal process was developed to convert dm+d terms into MHRA drugs dictionary terms, before processing through the MHRA pharmacovigilance database. Yellow Cards received by the MHRA PhV database with unmapped codes/terms are processed into a staging area. This area is monitored on a daily basis by a team of Signal Assessors who perform coding of adverse drug reactions and Yellow Cards on a daily basis. Once a suitable term is selected, it is stored as a mapping for any future Yellow Cards. In order that no information is lost at any mapping stage, the original term names (from the terminology used in the clinical system) are collected in the Yellow Card message. A quality audit process is being introduced to ensure mapping of terms between dm+d and MHRA drugs dictionary are appropriate.

# 7 Other Recommendations

This section provides recommendations for recording and reporting functionalities, strategies and initiatives in clinical systems for handling drug information in general, aimed at improving ICSR data management and PhV analysis.

## 7.1 Develop easy to use ADR recording and reporting functionalities in clinical systems

**The design of ADR ('suspected' or 'diagnosed') reporting functionalities in clinical systems should follow the clinicians workflow and use pre-populated information as much as possible.**

As discussed in section 4, documenting ADRs in clinical systems is an important activity in patient care. To improve documenting ADRs in the patient record, the design should follow a logical implementation in the clinician's workflow, preferably in a standardized way. While documenting the ADR, a trigger can be shown where the HCP can indicate if this information can also be sent to the PhV Centre. Other prompts to consider are stopping a medication because of an ADR or recording a drug sensitivity. Acknowledging that documenting an ADR starts with a clinical diagnosis, it is also important to provide a functionality that facilitates ADR reporting without such prompts. This will support reporting of true ‘suspicions’ where no ADR has been documented as such in the clinical record.

It is also recommended to pre-populate ADR reports with data from the EHR system. A valid ADR report will (as a minimum) provide information about the patient, the medication, the suspected ADR and the reporter. Since almost all EHR systems will have medication information, this is a prime candidate for pre-population. Most likely this will use the identifiers and descriptions for medication from a local or national patient care medicinal product dictionary, which will then require mapping to the PhV medication dictionary. Once IDMP identifiers will be used in ICSR transmissions, the medication information may need some further transformations by the PhV Centre, as illustrated in section 6. The special situations described in section 6.2 (e.g. medication error, interactions and parental exposure) highlight that ADR reports received from clinical systems may need careful attention when entering in PhV databases to ensure that the ICSR Drug Section will be populated correctly.

## 7.2 ADR reporting strategy; MHRA Best Practice

**Develop ADR reporting functionalities in clinical systems as part of an overall strategy, involving active cooperation with all parties responsible.**

Best practices of the MHRA to improve ADR reporting are highlighted in this section. In the UK, the MHRA suspected ADR reporting system is called the Yellow Card scheme (after the first yellow-coloured reporting forms) and the MHRA has a Yellow Card strategy; its key objective is **'to strengthen the reporting of suspected ADRs by increasing both the quantity and quality of reports'**. The Yellow Card strategy is based on four elements of education, promotion, facilitation and motivation that are underpinned by collaborations and partnership working with stakeholders. The same strategy was subsequently adopted as best practice for NCAs to improve their national ADR systems by Heads of Medicines Agencies (HMA) and the International Coalition of Medicines Regulatory Authorities (ICMRA) pharmacovigilance subgroup to improve adverse event reporting.

**Table 8: Four pillars of Yellow Card scheme**

| | |
|---|---|
| Education | Raising understanding about the purpose, value and importance of Yellow Card reporting, embedding in the Yellow Card scheme and PhV into health professional education programs, to make reporting of suspected ADRs a more visible aspect of the responsibilities of healthcare professionals |
| Facilitation | Making reporting easy and accessible to meet the needs of reporters e.g. electronic reporting and the use of technology |
| Promotion | Develop and maintain promotion and communication strategies and campaigns |
| Motivation | Making reporters more likely to report through approaches to incentivize reporting through acknowledgment and feedback |

To meet these objectives, improvements to the Yellow Card reporting website are periodically made to make it easier to report, educational modules produced for healthcare professionals, outreach work, establishment of regional centres and networks as well as regular targeted and traditional campaigns.

MHRA have also pioneered connecting their systems into clinical IT systems used by healthcare professionals. MHRA have integrated suspected ADR reporting into several primary care clinical system suppliers for GPs such as EMIS Web, SystmOne and Vision so that 93% of GP practices in the UK can report a Yellow Card directly from their patient management record systems (MHRA, 2020).

Through collaboration with their National Health Service (NHS) an information standard for the Yellow Card reporting was developed based around the ICH E2B(R2) standard. Important reporting fields, including the standard CIOMS reporting requirements, as well as added triggers to prompt users to report a suspected ADR were defined. The resulting workflow for the Yellow Card scheme is depicted in figure 16 for electronic reporting. This standard is available for implementation by any clinical IT system in healthcare. This Yellow Card information standard is now a core requirement for GP system suppliers to include so that their software have the capability for GPs and their practice team to report a suspected ADR directly to the MHRA Yellow Card scheme from their systems.

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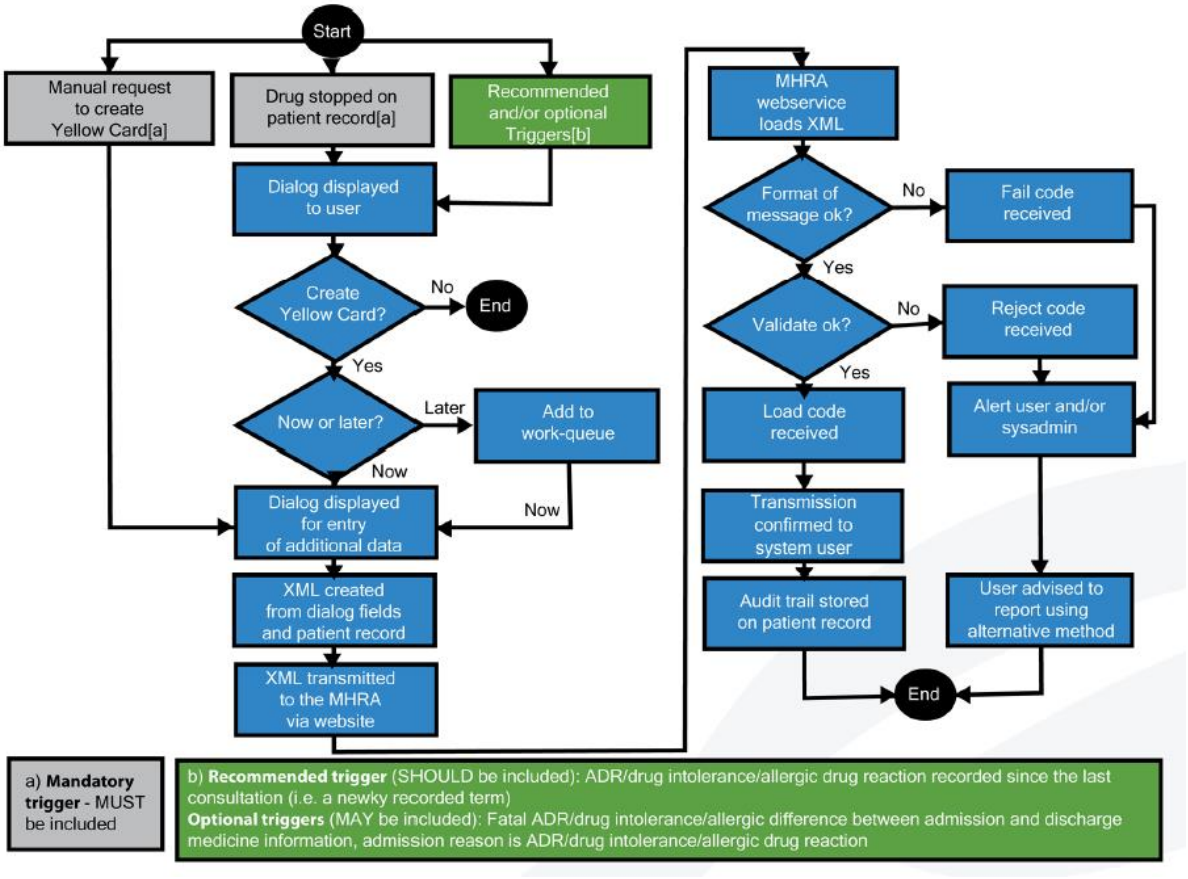


*Figure 16. The electronic Yellow Card reporting workflow from Scope WP4 (EMA, 2016)*

This approach for integration of ADR reporting within GP systems provided the foundation for other initiatives in clinical systems within the UK, for example in the clinical system for hospital pharmacists that provide medicines information and in some secondary care settings.

The MHRA has also redeveloped the technology used behind its reporting site and the mobile application for reporters. This technology uses Application Programming Interfaces (API), that is a set of defined rules that enable different applications to communicate with each other. It acts as an intermediary layer that processes data transfers between systems. As a result, MHRA recently launched a new and improved website platform with additional enhancements based on user feedback to give reporters a better, more tailored and transparent reporting experience. The functionality used will enable and offer new upgrades as well as new features in future such as:

- technology that helps keep you up-to-date with your report as it progresses through MHRA review process and enables you to update your reports.
- easier access to real-time safety communications and control over alerts, allowing you to switch on and off relevant safety communications.
- the ability to manage information about healthcare products via a product watch list.

- visualisation of data that will allow you to view information in a more user friendly, accessible way.
- for frequent reporters, a search functionality that will allow your previous reports to be found easily.
- tailored forms depending on different types of products being reported.
- periodic follow up for different types of products being reported.
- enable linkages between other applications such as the NHS app for patients and other sources of reference materials used by patients and healthcare professionals in future.

## 7.3 Utilize other IDMP identifiers for ADR reporting from clinical systems

### Explore exchange of PCIDs for ADR reporting from clinical systems

UNICOM Working paper 8.7 recommends that collection of information on the drugs could be improved by scanning a medicine package with a 2D-Data Matrix code or barcode capturing IDMP product identification. This would retrieve not only the MPID, but also obtain the Product Package Identifier (PCID), batch ID and serial number (figure 17). Scanning at the clinical point of care would facilitate accurate record keeping in the EHR and medication record.

The survey responses however show that if barcode scanning is used in clinical care, this would not always lead to providing detailed information about the drug when reporting ADRs, as this information is not always recorded at patient level. This observation is supported by literature, where relevance for PhV of supporting automated recording of product package information with electronic barcode scanning throughout the supply chain is emphasized. However, such technology transitions may take a long time and require full commitment from all stakeholders involved. (Klein, 2019)

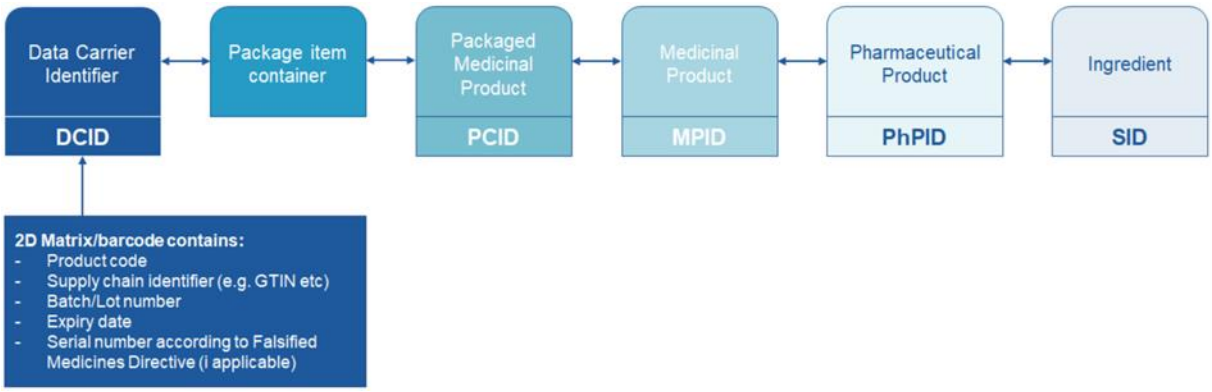


*Figure 17. Hierarchy of IDMP product identification*

When discussing the use of IDMP identifiers in ICSRs in Working paper 8.7, the focus has been on MPID and PhPID (+Substance ID) as these have dedicated data elements in the ICSR. UNICOM Working paper 9.2 explains that the packages are a key element for MPDs and in eHealth activities.

Whereas MPDs currently utilize their nationally defined package identifiers, there is a potential use of the IDMP equivalent of the PCID, and this is sometimes recorded at patient level.

Although the ICSR does not have a data element for PCID, it is recommended to explore transmission of the PCID or nationally defined package identifiers when reporting an ADR to a PhV centre. These package identifiers could then subsequently be used to retrieve other identifying drug information that fit with the ICSR drug data elements (MPID, name parts).

It could be considered to incorporate barcode scanning functions not only at clinical point of care, but also in ADR data collection tools used by patients (e.g., ADR reporting app) (Fukushima, 2022). Alternatively, this can be mimicked by adding a photo (upload) functionality in an electronic ADR reporting webform or app. The photo of the barcode can be used by the PhV centre to retrieve detailed drug information (figure 18).


*Figure 18. Visualisation of patient accessing medication identifiers via barcode scanning*

## 7.4 Mapping clinical terminologies

### Facilitate mapping of terms between different clinical terminologies

Integration of clinical systems with ADR reporting systems requires transmission of data elements within the ADR report to the NCAs ADR database. By EU law, medicine regulators and pharmaceutical industry

are required to use the MedDRA® terminology[1] in ICSR transmissions to code reactions/events, medical history (diagnoses, surgical procedures), reported cause of death, laboratory terms and indication for drug use. MedDRA has become the standard medical terminology for drug regulators and pharmaceutical companies in the ICH regions. The transmitted data from clinical systems does not necessarily follow the same clinical terminology, as clinical systems often use SNOMED CT or another terminology. Mapping is a solution to cope with this difference and can facilitate an efficiency gain in processing ADR reports to the PhV database.

MedDRA is compatible with for example CTCAE (Common Terminology Criteria for Adverse Events) used in oncology and has mappings in place with SNOMED CT and ICD-10. Development work is ongoing for a bi-directional mapping with ICD-11. When no mapping exists between MedDRA and the clinical terminology used, a strategy can be developed similar to the one described for the drug dictionaries used in UK (section 7.3).

The SNOMED CT- MedDRA mappings are updated annually as a product of a collaborative agreement between SNOMED International and ICH and include two independent maps (MedDRA to SNOMED CT -and- SNOMED CT to MedDRA) which have been derived from frequently used key PhV MedDRA terms identified from databases from the European Medicines Agency (EMA) and the UK MHRA.

**MedDRA to SNOMED CT (6,467 records)**

| | A | B | C | D |
|---|---|---|---|---|
| 1 | MedDRA Code | MedDRA LLT | SNOMED Code | SNOMED FSN |
| 2 | 10000051 | Abdominal aneurysm | 233985008 | Abdominal aortic aneurysm (disorder) |
| 3 | 10000054 | Abdominal aortic aneurysm | 233985008 | Abdominal aortic aneurysm (disorder) |
| 4 | 10002338 | Aneurysm of abdominal aorta | 233985008 | Abdominal aortic aneurysm (disorder) |
| 5 | 10048746 | Abdominal bloating | 116289008 | Abdominal bloating (finding) |
| 6 | 10009881 | Colic | 9991008 | Abdominal colic (finding) |
| 7 | 10000059 | Abdominal discomfort | 43364001 | Abdominal discomfort (finding) |
| 8 | 10054209 | Gastrointestinal discomfort | 43364001 | Abdominal discomfort (finding) |
| 9 | 10000060 | Abdominal distension | 162068007 | Abdominal distension symptom (finding) |
| 10 | 10000075 | Abdominal hysterectomy | 116141005 | Abdominal hysterectomy (procedure) |

MedDRAToSnomedMaps | SNOMEDToMedDRAMaps

**SNOMED CT to MedDRA (3,729 records)**

| | A | B | C | D |
|---|---|---|---|---|
| 1 | SNOMED Code | SNOMED FSN | MedDRA Code | MedDRA LLT |
| 2 | 233985008 | Abdominal aortic aneurysm (disorder) | 10000054 | Abdominal aortic aneurysm |
| 3 | 116289008 | Abdominal bloating (finding) | 10048746 | Abdominal bloating |
| 4 | 9991008 | Abdominal colic (finding) | 10000055 | Abdominal colic |
| 5 | 43364001 | Abdominal discomfort (finding) | 10000059 | Abdominal discomfort |
| 6 | 162068007 | Abdominal distension symptom (finding) | 10000060 | Abdominal distension |
| 7 | 116141005 | Abdominal hysterectomy (procedure) | 10000075 | Abdominal hysterectomy |
| 8 | 21522001 | Abdominal pain (finding) | 10000081 | Abdominal pain |
| 9 | 43478001 | Abdominal tenderness (finding) | 10000097 | Abdominal tenderness |
| 10 | 177250006 | Abdominoplasty (procedure) | 10053774 | Abdominoplasty |

MedDRAToSnomedMaps | SNOMEDToMedDRAMaps

*Figure 19. MedDRA - SNOMED CT mapping examples (ICH, 2021)*

[1] MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA® trademark is registered by ICH.

## 7.5 Other initiatives to improve ADR collection

### Consider initiatives besides integration to improve PhV reporting with information from clinical systems

If integrating ADR reporting functions in the clinical system provides difficulties, other initiatives should also be considered to improve PhV reporting using the available information in clinical systems. It is possible to use clinical system information in a different fashion as illustrated in the Portuguese initiative and Dutch initiative described in the grey box below. The Dutch NCA described an initiative where ADR reporting functionalities are not integrated in the clinical system, but active pulling of data regarding ADRs through querying the hospital system is conducted by the NCA in collaboration with the health care professionals.

**Dutch pilot - query system**

If a potential signal is detected via the spontaneous reporting system, the Netherlands Pharmacovigilance Centre Lareb can reach out to hospitals who will run a targeted query in structured and unstructured data in the EHR-database for that particular drug-event combination of interest. Hospital staff may find additional cases in the EHR and the hits of the query are verified whether they are potential ADRs. The result of such a query provides standardized text according to the national MPD used in clinical care (G-standaard); the drug information is provided as substance with pharmaceutical form and strength (these are presented as separate entities). If available (e.g. for biologicals), the batch number will be provided as well. There is no automated dataflow thus data entry in the PhV database requires manual work.

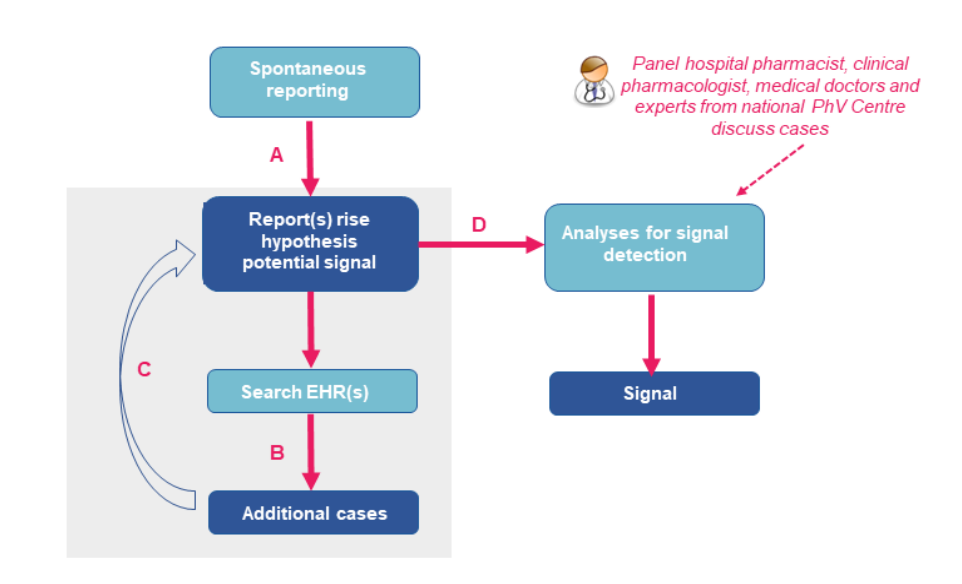


*Figure 20. Dutch pilot for querying hospital systems for ADR reports contributing to potential signals*

The Portuguese NCA mentioned a Risk Management System which has the opportunity to send ADR cases collected in this clinical system directly to the PhV centre.

Both initiatives thus do not have an integration in place, but do provide additional ADR reports to the PhV centre. Such options can be considered as a first step to explore if the clinical system can provide additional ADR reports, before integration of ADR reporting functionalities in clinical systems, or as an alternative if integration is not considered feasible at that moment due to barriers.

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# 9 Appendix

This appendix aims to provide a basic understanding of the interplay between IDMP identifiers, name part data elements and ICSR messages, using excerpts from UNICOM Working paper 8.7 'IDMP Coding Principles and Guidance for ICSRs'. This may be particularly relevant to readers who are not familiar with the ICSR message.

## A.1 Relationship ICSR - IDMP

As from 30 June 2022, Marketing Authorisation Holders and EU medicine regulators are required to use the International Organisation for Standardization (ISO) ICSR 27953-1 (2011) standard for the submission of suspected ADR reports to EudraVigilance[2] (in line with Article 26(2)(a) of the Commission Implementing Regulation (EU) No 520/2012). The modalities on how to implement and apply the ISO ICSR standard are defined in the International Council for Harmonisation (ICH) E2B(R3) documentation (ICH, 2023). This ISO ICSR message in ICH E2B(R3) format is also used for the exchange of ADR reports between the EMA and WHO Uppsala Monitoring Centre (WHO UMC).

The initial receipt of a suspected ADR may not be in ICSR format, but subsequent exchanges between medicine regulators, pharmaceutical industry and WHO-UMC use the ISO ICSR message in ICH E2B(R3) format. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction, and at least one suspect (or interacting) medicinal product. Upon receipt of a suspected ADR, the verbatim (literal term used by the reporter or provided via the reporting mechanism) of a medicinal product can contain different levels of precision, depending on the source and method of collection. The ICSR format has placeholder data-elements for providing information on the medicinal product(s) in line with ISO standards for the Identification of Medicinal Products (IDMP). Until the relevant IDMP terminologies and identifiers become available and are agreed for use in the ICSR message, free text can be used in the ICSR to describe medicines, both for the suspect (interacting) product and for any concomitant medications.

## A.2 ICSR Drug Section

The ICH E2B(R3) ICSR structure is shown in Figure 21. Identifiers resulting from the implementation of ISO IDMP identifiers are relevant for ICSR Section D (Patient characteristics, more specifically data elements for ‘Relevant Past Drug History’ and ‘Relevant Past Drug History of Parent’) and Section G (Drug(s) information).

[2] EudraVigilance is the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or are being studied in clinical trials in the European Economic Area (EEA). The EMA operates the system on behalf of the EU medicines regulatory network.

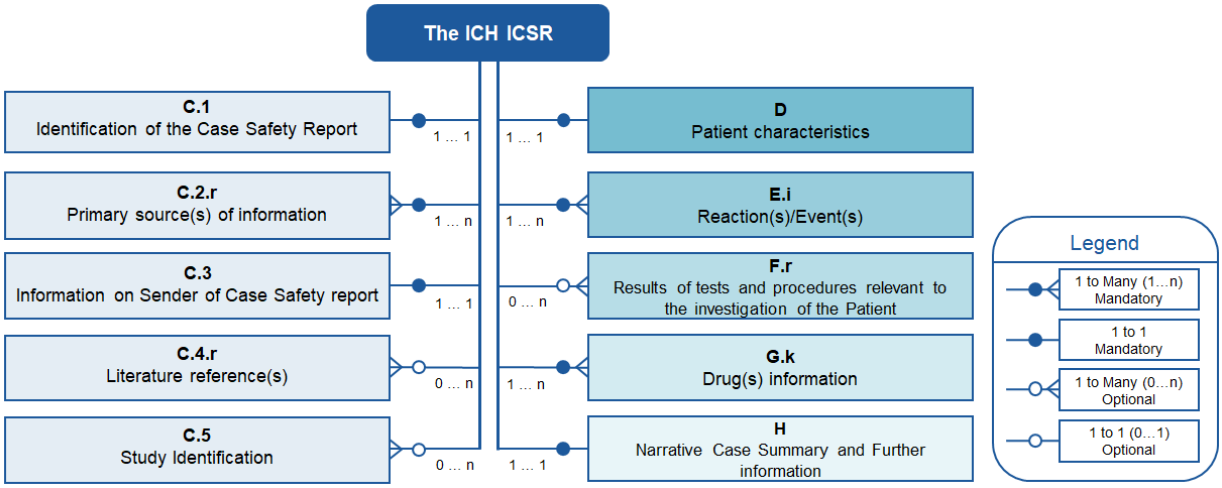


*Figure 21. ICH E2B(R3) ICSR structure*

The following table (table 9) summarises the ICSR data elements relevant for ISO IDMP identifiers and their corresponding IDMP standards:

**Table 9. ICSR data elements relevant for ISO IDMP identifiers**

| ICH E2B(R3) Section | ICH E2B(R3) Element id | Element Name | ISO standard |
|---|---|---|---|
| D. Patient Relevant Past Drug History | D.8.r.2b | Medicinal Product Identifier (MPID) | 11615 |
| D. Patient - Relevant Past Drug History | D.8.r.3b | Pharmaceutical Product Identifier (PhPID) | 11616 |
| D. Patient- Relevant Past Drug History of Parent | D.10.8.r.2b | Medicinal Product Identifier (MPID) | 11615 |
| D. Patient- Relevant Past Drug History of Parent | D.10.8.r.3b | Pharmaceutical Product Identifier (PhPID) | 11616 |
| G. Drug(s) Information | G.k.2.1.1b | Medicinal Product Identifier (MPID) | 11615 |
| G. Drug(s) Information | G.k.2.1.2b | Pharmaceutical Product Identifier (PhPID) | 11616 |
| G. Drug(s) Information | G.k.2.3.r.2b | Substance/Specified Substance TermID | 11238 |
| G. Drug(s) Information | G.k.4.r.9.2b | Pharmaceutical Dose Form TermID | 11239 |
| G. Drug(s) Information | G.k.4.r.10.2b | Route of Administration TermID | 11239 |
| G. Drug(s) Information | G.k.4.r.11.2b | Parent Route of Administration TermID | 11239 |

ICSR section G.k. Drug(s) Information covers both suspect and concomitant medications, including drugs suspected to have a type of interaction.

A minimum of one suspect/interacting medication needs to be provided for each valid ICSR. Medications used to treat the reaction/event should not be included here. The full ICH E2B(R3) Section G. Drug(s) information (including Name Parts as an EU extension) is shown in figure 22.

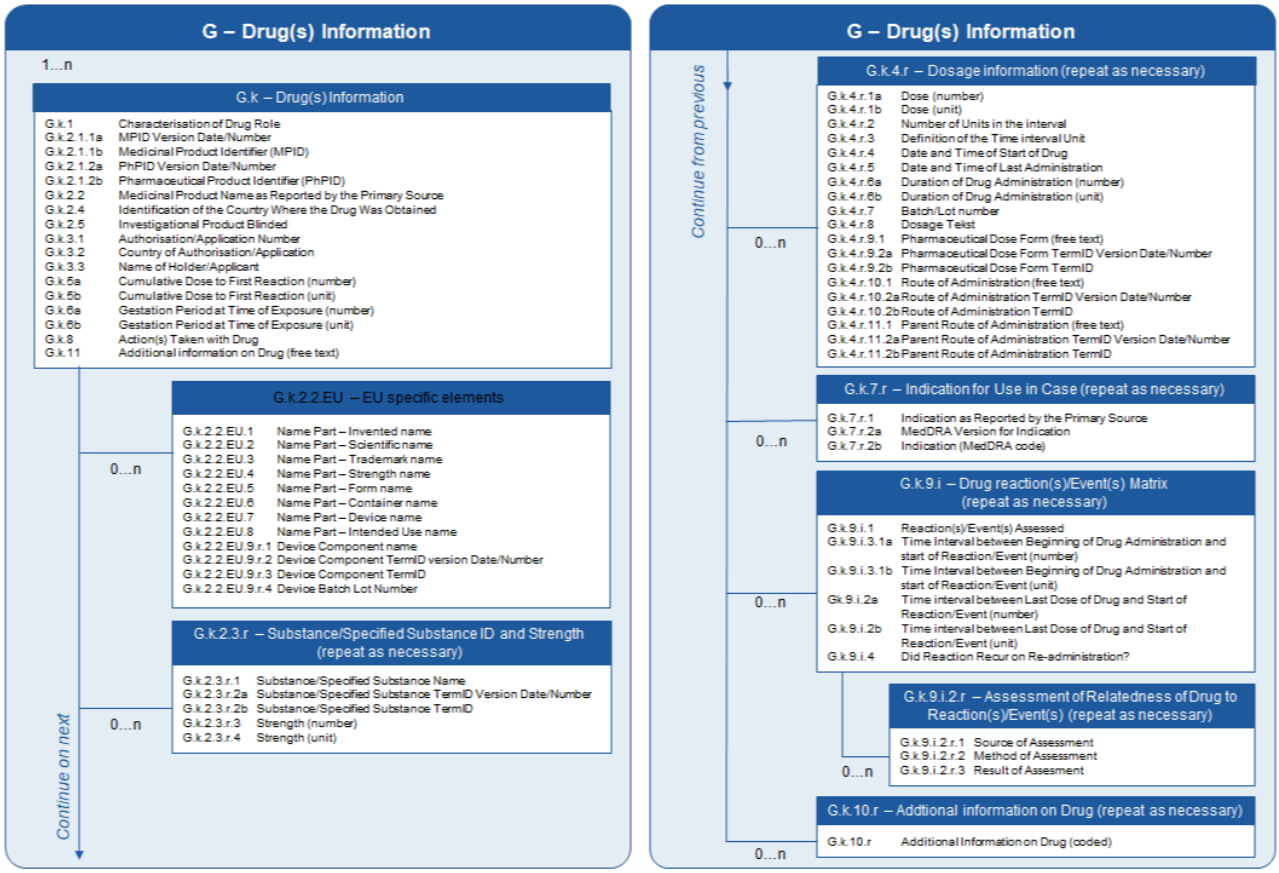


*Figure 22. Full ICH E2B(R3) Section G. Drug(s) information*

## A.2.1 Name parts

Medication name parts are a means of specifying the name of a medicinal product as separate components. This allows for input name strings to be automatically matched to possible medical products, rather than through manual classification activities. Populating ICSR name part elements is considered useful when no PhPID can be selected, or when a PhPID can be selected but more details of the medicinal product name are known.

Use of name parts in the ICSR has not been agreed worldwide at the level of ICH E2B(R3), but is an EU regional extension of the ICSR specification. Extensive information on the name parts is provided in the EU ICSR implementation Guide (EMA, 2021). The following name parts are available in the ICSR (table 10):

**Table 10. ICSR name parts**

| Concept Name | Concept code | Example |
|---|---|---|
| Container name | CON | Pre-filled syringe |
| Device name | DEV | InjectPen |
| Form name | FRM | Soft capsules |
| Invented name | INV | TotalFlu |
| Scientific name | SCI | For TotalFlu: Influenza vaccine (surface antigen, inactivated, prepared in cell culture) |
| Strength name | STR | 50mg |
| Trademark name | TMK | Syncopharm |
| Intended use name | USE | For multiCure Heartburn relief: heartburn relief |

## A.3 ISO IDMP standards

IDMP aims to uniquely identify and exchange information on medicinal products. It consists of several levels of identification, with their own ISO standards and Technical Specifications (implementation guides). Below, a concise overview of the relevant ISO IDMP standard is provided, with a brief introduction on use of the resulting IDMP identifiers and terminology in the ICSR.

| ISO 11238 - Substances |
|---|
| Medicinal products consist of substances which can be active ingredients, excipients, or constituents (e.g., impurities, degradants, extraction solvents, vehicles, active markers). There are two levels of ingredients: Substance and Specified Substance, which are further defined by several attributes, including whether the substance is a chemical, protein, nucleic acid, polymer, or structurally diverse (e.g., tissue, gene, blood). Specified Substances can have further attributes, such as grade or purity, manufacturing information and specifications. Once a substance has been defined, a unique (global) identifier (ID) can be assigned and maintained in a (global) system. The ICSR contains a data-element (ICH E2B(R3) - G.k.2.3.r.2b) to provide a (specified) substance ID (SID). The SID should be provided in the ICSR when a PhPID does not exist, but a substance name has been assigned an ID, and is known by the sender e.g., for investigational medicinal products or excipients. If a MPID, PhPID or SID is not available, but the Substance name is known, then this can be entered as free text in the data element (ICH E2B(R3) -G.k.2.3.r.1). For this Deliverable, which is limited to post-authorization ICSRs (similar to UNICOM D8.7), it is assumed that all active substances will have a corresponding PhPID as well, and that further guidance on providing (specified) SIDs in the ICSR would not be needed. |

| ISO 11240 – Units of Measurement |
| --- |
| This standard defines that the Unified Code for Units of Measure (UCUM) standard, an existing standard for units of measurement, is used to define the strength of medicinal products. UCUM is already an integral part of the ISO ICSR standard, and the ICH E2B(R3) Implementation Guide explains how to use UCUM in the ICSR message (ICH, 2016). ICH has also published a list of UCUM units for use in the ICH E2B(R3) drug dosage and cumulative dosage data elements.<br><br>UCUM specifies the usage of an algorithm to validate the correct format of a unit. To support stakeholders, a list of valid laboratory test units has been published for use in the EU as the UCUM algorithm does not indicate whether the unit is appropriate for the ICSR data element being used (e.g., lab test result unit being used in a drug dosage data element). |

| ISO 11239 - Pharmaceutical dose forms, units of presentation, routes of administration and packaging |
| --- |
| This standard describes the controlled terminologies to use to characterise pharmaceutical dosage form, routes of administration, units of presentation and packaging. Of these, only pharmaceutical dose forms and routes of administration are relevant for the ICSR message. The Routes of Administration and Dosage Form terms in the European Directorate for the Quality of Medicines (EDQM) Standard Terms (ICH, 2020) database comply with the ISO 11239 standard. ICH selected EDQM as the maintenance organization for the Dosage Forms and Routes of Administration terms for human medicinal products to be used in ICSRs.<br><br>ICH published supplementary information on the use of EDQM terms in the electronic exchange of ICSRs according to the ICH E2B(R3) Implementation Guide (ICH, 2016). Use of EDQM terms for Dosage forms and Routes of administration has become mandatory as of 30 June 2022 in relation to reporting obligations to the EMA EudraVigilance database. |

**ISO 11616 – Pharmaceutical Product Identifier**

This standard describes the use of PhPIDs. It defines the data elements, structures and relationships between data elements that are required for the exchange of regulated information, in order to uniquely identify pharmaceutical products. Each pharmaceutical product has a set of PhPIDs. A PhPID uniquely associates medicinal products with the same or similar pharmaceutical composition. The PhPID, or more correctly a set of PhPIDs, is generated by an algorithm using the Substance ID (SID), the pharmaceutical dose form ID and the (reference) specific strength.

The PhPID plays a central role for IDMP implementations, since it provides an abstract level to link medicinal products. The same PhPIDs will be assigned to all medicinal products that have the same characteristics including substance, dosage form and strength, separate from any other details such as regulatory authorisation, organisation, packaging or naming and regardless of where they were authorized.

The PhPID can be specified at various levels of detail for a given pharmaceutical product.

| PhPID level | PhPID set for substance base | PhPID set for substance with salt |
|---|---|---|
| PhPID L1 | Ibuprofen | Ibuprofen lysine |
| PhPID L2 | Ibuprofen 400mg | Ibuprofen lysine 684mg<br>(equivalent to ibuprofen 400mg) |
| PhPID L3 | Ibuprofen tablet | Ibuprofen lysine tablet |
| PhPID L4 | Ibuprofen 400mg tablet | Ibuprofen lysine 684mg<br>(equivalent to ibuprofen 400mg) tablet |

The ICSR has dedicated data-elements for capturing the PhPID, regardless of the level and underlying details used to generate the PhPIDs.

**ISO 11615 – Medicinal Product Identifier**

This standard describes the use of MPIDs. The MPID uniquely identifies a medicinal product, reflecting (but not replacing) any other authorization numbers allocated by a regulator. The 11615 ISO standard describes the detailed data elements and their structural relationship required for the unique identification of regulated medicinal products. Data elements that identify and characterize a medicinal product include the product name (authorised by regulatory agency), clinical particulars (e.g., indications, contraindications), pharmaceutical product (substance, dosage form, route of administration), medicinal product packaging, marketing authorisation (e.g., authorisation number, application information), and manufacturer/establishment. The MPID is the most precise level of identifying the product given to the patient in the ICSR (except for the batch number).

Triggers to assign a new MPID (based on ISO 11615 version 2015) are:

- Marketing authorization in relation to the jurisdiction;
- Legal status of supply (e.g., prescription only or “over the counter” sale);
- Medicinal Product name;
- The pharmaceutical dose form;
- The ingredient substance(s) and their strength;
- Device(s) where a Medicinal Product is combined with a medical device and where the pharmacological, immunological or metabolic action should be considered as the principal mode of action; the medical device is presented as part of the Medicinal Product;
- Therapeutic indication(s) as authorized for the Medicinal Product

According to the EU ICSR Implementation Guide, MPIDs should only be used when the information provided by the primary source includes the MPID or if enough information is provided by the primary sources that the correct MPID can be selected unambiguously. The lack of stability of an MPID and the complexity of its constitution means that many drug verbatims cannot have an MPID accurately coded based on the information provided if more than 1 MPID would be available for that product.

ISO standard 11615 also describes the use of a Packaged Medicinal Product Identifier (PCID), which uniquely identifies a medicinal product based on its packaging. The ICSR does not have a dedicated data element for package identifiers.

## A.4 Current guidance in ICH and EU ICSR Implementation Guides

Both the ICH E2B(R3) Implementation Guide (ICH, 2023) and the EU ICSR Implementation Guide (EMA, 2021) provide basic guidance on how to populate the ICSR drug section using MPIDs, PhPIDs or Substance IDs. As a general principle, the most precise structured information should be provided when identifying medicinal products and redundant information does not have to be repeated. For example, if a MPID is provided, there is no need to provide a PhPID. Likewise, if a PhPID is provided, there is no need to provide information for substance. The decision tree provided in figure 23 should be used for entering medicinal product information in the relevant E2B(R3) drug data elements.

Although the free text 'Medicinal Product Name as Reported by the Primary Source' (E2B(R3) G.k.2.2) is a mandatory data element, the sender of the ICSRs should attempt to code the verbatim text using ISO IDMP identifiers where possible. If appropriate, structured name parts should be provided as well. If the sender can answer 'yes' to a question listed in the diagram below this is the information that should be provided in the ISO ICSR message in addition to the product name as provided by the primary source. If the answer is 'no' then the sender should progress to the next question (figure 23):

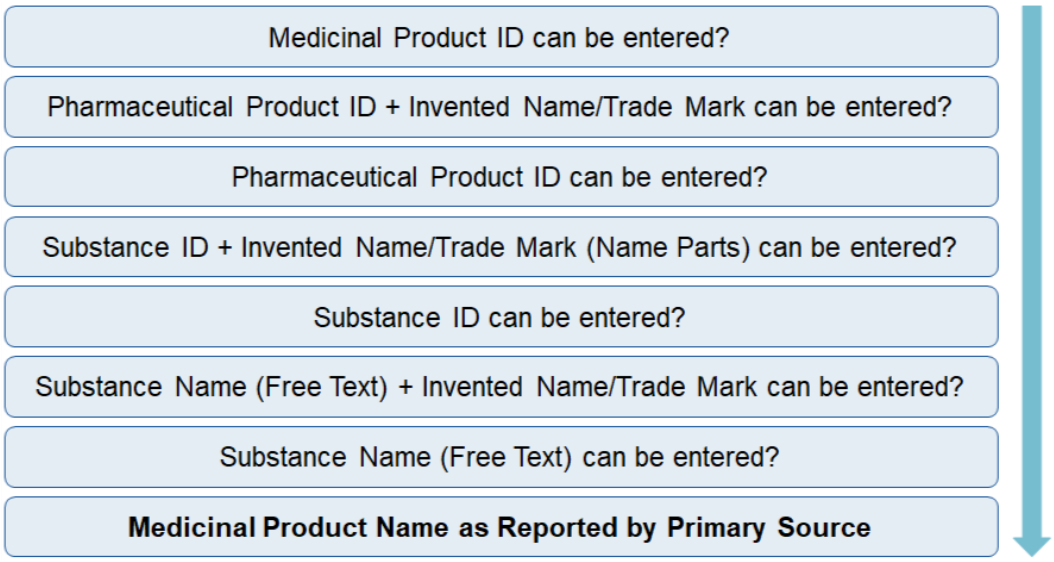


*Figure 23. EU ICSR decision tree for entering medicinal product information*