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Health informatics — Requirements for medication safety alerts

Informatique de santé — Exigences relatives aux alertes de sécurité sur les médicaments

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 215, *Health informatics*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 251, *Health informatics*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

To improve the quality and safety of patient care in digital work-flow environments, computer assisted clinical decision support systems (CDSSs) have been emphasized and implemented in healthcare organizations and pharmacies, especially focusing on medication safety.

CDSSs for medication safety have been developed and used in many countries as an essential component for decision support for clinicians in prescribing, dispensing and administering medication in connection with an electronic health record (EHR), computerized physician order entry (CPOE) system or pharmacy electronic health record (PEHR) and digitized knowledge bases.

Depending on the availability of knowledge bases and functionalities, CDSS can be classified into four types[12]:

Type 1 CDSS: provides categorized information that requires further processing and analysis by users before a decision can be made. This type of decision support includes direct access to relevant information, such as web-based access to current rules for travel inoculation.

Type 2 CDSS: presents the clinician with trends of a patient's changing clinical status and alerts clinicians to out-of-range assessment results and intervention strategies. Clinicians are prompted to review information related to the alerts before arriving at a clinical decision.

Type 3 CDSS: uses deductive inference engines to operate on a specific knowledge base and automatically generate diagnostic or intervention recommendations based on changing patient clinical condition, with the knowledge and inference engines stored in the knowledge base. These systems include systems that consider the disease and medication of the patient and whether these have contraindications for new medication. These systems require computer-readable rules and an underlying computer EHR system that is also computer processable. They also require computerized terminological representation of clinical concepts.

Type 4 CDSS: uses more complex knowledge management and inference models than the other three decision support types. These systems include case management reasoning, neural networks and statistical discrimination analysis to perform outcome or prognostic predictions. Such systems possess self-learning capabilities and use fuzzy set formalism and similarity measures or confidence level computation as mechanisms to deal intelligently and accurately with uncertainty.

Among the four types of CDSS, type 3 has been focused on developing CDSS for medication safety alerts in the countries where EHRs are in use, though type 4 is available in some countries.

Since the primary purpose of a medication CDSS implementation is the prevention of potential harmful effects of medication or errors, all types of CDSS have been designed to have the functionality of alerting or warning clinicians in a prospectively actionable fashion for all settings.

However, the desired outcome of prevention of harmful drug therapy with the use of CDSS for medication safety has not been clearly defined. This can be attributed to factors such as poor and varied stratification (mainly due to lack of clear consensus on terminology and rules) of safety risk warnings or alerts. In addition, alert fatigue (the result of frequent alerts to clinicians which are not clinically significant or tailored to speciality interests) is known to be one of the major factors contributing to alert overrides, which can result in serious clinical consequences.

Unclear content and verbose language in medication safety alerts can also be barriers to clear communication with clinicians of the clinical significance of potential safety risks.

In addition, since the alerts are linked to the embedded CDSS knowledge base through specifically designed algorithms, the differences between algorithms to produce alerts, even though they are based on the same knowledge base, can be another inhibiting factor in getting uniform and maximal benefit from safety alert systems operating on the same patient population with the same clinical condition or situation.

In the USA, a number of EHR and CPOE vendors, as well as several drug knowledge bases, are in use with wide differences in content, alert types and displays. Medication safety alerts in computerized information systems have typically been developed for pharmacy software, often in connection with pharmacy benefit management, the requirement for a prospective drug utilization review (DUR) programme for outpatients using a prescription filling service in community pharmacies, or both. For prospective DUR programmes, the potential medication problem types for medication safety alerts were defined by federal regulation and have been used for developing CDSS for pharmacy practitioners and CPOE by system vendors.

In the Republic of Korea, a number of drug knowledge bases (in the form of CDSS) with the functionality of safety alerts which are developed by system vendors and pharmacy benefit managers of national health insurance bodies are in use, mostly benchmarking the prospective DUR programme in the USA. However, they are not detailed enough to meet individual use cases and thus healthcare organizations resort to commercial vendors for more in-depth and user-friendly coverage of medication alert content.

In other countries, various types or methods for providing medication safety alerts in connection with digitized knowledge bases have been developed and implemented in digitized health information systems. However, there are no internationally or regionally standardized requirements for improving patient safety by alerting healthcare professionals to potential safety risks.

Given the wide variability of medication safety alert content and implementation approaches across different system vendors and drug knowledge bases, there is a need for medication alert standardization both nationally and internationally.

Stakeholders can use this document for developing common and structured medication safety alert systems to improve patient safety.

The actors included in the scope of this document include, but are not limited to:

— healthcare organisations which deploy EHR or PEHR systems incorporating medication safety alerts;

— vendors and implementors of systems with medication safety alerts or those who provide information for the alerts, such as:

  — CDSSs

  — EHRs

  — pharmacy systems

  — clinical information systems

  — practice management systems (EHR-like systems for individual or small-group settings).

Health informatics — Requirements for medication safety alerts

1 Scope

This document specifies the requirements for medication safety alert systems and the topics which are relevant to alert system vendors. This document applies to clinical decision support systems (CDSSs) whether or not these are medical devices.

This document addresses:

— requirements for terminology used in medication safety alerts;

— requirements for choosing a knowledge base for medication safety alert systems;

— requirements for the proper functionality of CDSSs as related to medication safety alert systems;

— requirements for medication safety alert display;

— requirements for quality measurements to improve the effectiveness of medication safety alerts.

The following are out of the scope of this document:

— the development of content (rule-based knowledge base) for CDSS;

— the development of algorithms for generating medication safety alerts in CDSS;

— the development of alert processors for medication safety alerts in CDSS.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO/TS 22756, *Health informatics — Requirements for a knowledge base for clinical decision support systems to be used in medication related processes*

ISO 27789, *Health informatics — Audit trails for electronic health records*

IEC 82304-1, *Health software — Part 1: General requirements for product safety*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
administration
(self-) administering a (prescribed) medicinal product to the patient, using a specified method, and via a defined route, and recording that the act has actually happened at a particular date and time

[SOURCE: ISO/TS 19256:2016, 3.1, modified]

3.2
clinical decision support
CDS
software system that assists healthcare providers in making medical decisions

Note 1 to entry: These types of systems typically require input of patient-specific clinical variables and as a result provide patient-specific recommendations.

[SOURCE: ISO/TR 14639-2:2014, 2.8, modified]

3.3
clinical decision support system
CDSS
software that is designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base

Note 1 to entry: Patient-specific assessments or recommendations are then presented to the clinician or the patient to aid in the process of making evidence-based clinical decisions.

[SOURCE: ISO/TS 22756:2020, 3.2, modified]

3.4
dispensing
process by which an individual healthcare provider takes in a prescription, assesses that prescription, selects the prescribed medicinal product and delivers that medicinal product to the subject of care or their representative

Note 1 to entry: In most cases, but not necessarily always, the individual healthcare provider concerned will be a Pharmacist.

[SOURCE: ISO/TS 19256:2016, 3.9]

3.5
dispenser
specialization of a healthcare professional which is a representation of an individual professionally responsible for filling/dispensing the prescription

Note 1 to entry: The dispenser is usually a pharmacist but can be other individuals according to local jurisdiction.

[SOURCE: ISO 21549-7:2016, 3.5, modified]

3.6
drug (pharmacy) and therapeutics committee
DTC
forum to bring together all stakeholders involved in decisions about drug use

Note 1 to entry: The described forum can exist at any level within the health-care system – at district level (overseeing primary health-care facilities), in hospitals, or at the national level.

[SOURCE: *Drug and Therapeutics Committee – A Practical Guide*. World Health Organization, 2003]

3.7
drug utilization review
DUR
authorized, structured, ongoing review of healthcare provider prescribing, pharmacist dispensing and patient use of medication

[SOURCE: Academy of Managed Care Pharmacy – Managed Care Glossary]

3.8
electronic health record
EHR
logical representation of information regarding or relevant to the health of a subject of care

[SOURCE: ISO/TS 13972:2015, 2.24]

3.9
formulary list
list of medicines approved for use in a specific health-care setting

[SOURCE: *Drug and Therapeutics Committee – A Practical Guide*. World Health Organization, 2003]

3.10
formulary system
principles, criteria, procedures and resources for developing, updating and promoting the formulary (essential medicines) list

[SOURCE: *Drug and Therapeutics Committee – A Practical Guide*. World Health Organization, 2003]

3.11
knowledge database
system in which knowledge on a specific topic is specified as a set of declarative statements, hierarchical organization of such statements, and relationships between declarative statements, which serves as the underpinning of decision support systems

[SOURCE: ISO/TS 19256:2016, 3.19]

3.12
medication history
record keeping of the specificities of the prescribed/dispensed/OTC medicinal product (e.g. identification, brand, type, form, quantity, dosage)

Note 1 to entry: this record contains the medication still in use as well as the medication no longer in use.

[SOURCE: ISO/TS 19256:2016, 3.23, modified]

3.13
medication safety
freedom from preventable harm with medication use

[SOURCE: ISMP Canada, 2007, available at https://www.ismp-canada.org/definitions.htm#:~:text=Medication%20Safety%3A,did%20not%20reach%20the%20patient]

3.14
medication use evaluation
performance improvement method that focuses on evaluating and improving medication use processes with the goal of optimal patient outcomes

Note 1 to entry: medication use evaluation may be applied to a medication or therapeutic class, disease state or condition, a medication-use process (prescribing, preparing and dispensing, administering and monitoring) or specific outcomes.

[SOURCE: ASHP Guidelines on Medication-Use Evaluation, available at https://www.ashp.org/-/media/assets/pharmacy-informaticist/docs/sopit-formulary-guideline-medication-use-evalutation.ashx?la=en]

3.15
medicinal product
substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions

[SOURCE: ISO 11615:2017, 3.1.50, modified]

3.16
monograph
<medicinal products> written, unbiased evaluation of a specific medication

Note 1 to entry: Such a document includes the drug name, therapeutic class, pharmacology, indications for use, summary of clinical trials, pharmacokinetics/dynamics, adverse effects, drug interactions, dosage regimens and cost.

[SOURCE: ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System, available at https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines/gdl-pharmacy-therapeutics-committee-formulary-system.ashx]

3.17
overutilization
use of a drug in a quantity, strength or duration that is greater than necessary to achieve a desired therapeutic goal or that puts the recipient at risk of a clinically significant undesirable effect, or both

[SOURCE: US CFR 42§456.702, available at https://www.govinfo.gov/content/pkg/CFR-2011-title42-vol4/pdf/CFR-2011-title42-vol4-sec456-702.pdf]

3.18
pharmacy electronic health record
PEHR
logical representation of information regarding or relevant to the health of a subject of care in pharmacies in community or organized healthcare organizations

[SOURCE: Pharmacy Health Information Technology Collaborative HL7 EHR-System for a Pharmacist/Pharmacy Electronic Health Record Implementation Guide for Community Practice, available at https://www.hl7.org/documentcenter/public/standards/informative/13-294_HITSbook_HL7_Web.pdf]

3.19
predetermined standard
criteria and standard that has been established in accordance with the requirements of a drug use review programme

[SOURCE: US CFR 42§456.702, available at https://www.govinfo.gov/content/pkg/CFR-2011-title42-vol4/pdf/CFR-2011-title42-vol4-sec456-702.pdf]

3.20
prescribing
creating a prescription

[SOURCE: ISO/TS 19256:2016, 3.33]

3.21
prescription
direction created by an authorized healthcare person to instruct a dispensing agent regarding the preparation and use of a medicinal product or medicinal appliance to be taken or used by a subject of care

Note 1 to entry: The term "prescription" alone should be avoided as it is colloquially used at random for the following terms: new prescription message, prescription set and prescription item. Further, it is also used to describe a prescription form. The use of the terms prescription set, prescription item and new prescription message where appropriate is recommended.

[SOURCE: ISO/TS 19256:2016, 3.34]

3.22
screening
process of inspecting data for errors and correcting them prior to doing data analysis

Note 1 to entry: The screening can involve checking raw data, identifying outliers and dealing with missing data.

[SOURCE: Business Dictionary, WebFinance Inc.]

3.23
substance
matter of defined composition that has discrete existence, whose origin may be biological, mineral or chemical

[SOURCE: ISO 11238:2018, 3.84, modified]

3.24
underutilization
use of a drug by a beneficiary [recipient] in insufficient quantity, strength or duration to achieve a desired therapeutic goal or that puts the recipient at risk of a clinically significant undesired effect, or both

[SOURCE: US CFR 42§456.702, available at https://www.govinfo.gov/content/pkg/CFR-2011-title42-vol4/pdf/CFR-2011-title42-vol4-sec456-702.pdf]

4 Abbreviated terms

CPOE	computerized physician order entry
DDI	drug–drug interaction
IDMP	identification of medicinal products
MPD	medicinal product dictionary
ORCA	operational classification
PBM	pharmacy benefit manager

5 Requirements

5.1 General

This document applies to medication safety alerts which will be prospectively presented to healthcare providers at the point of care during medication use processes in clinical settings where a digitized health information system is operational to manage medication therapy for patient care.

The prospective safety alerts are displayed on visually verifiable devices before medication is prescribed, dispensed or administered to the patients, whereas the retrospective alerts occur after the patient has received the medication.

Since the ultimate goal of medication safety alerts is to prevent adverse drug reactions (ADRs) and ineffectiveness of the drug by minimizing or preventing medication and device error as depicted in Figure 1, this document focuses on drug use processes at any time before the prescribed medication is actually administered to the patient.

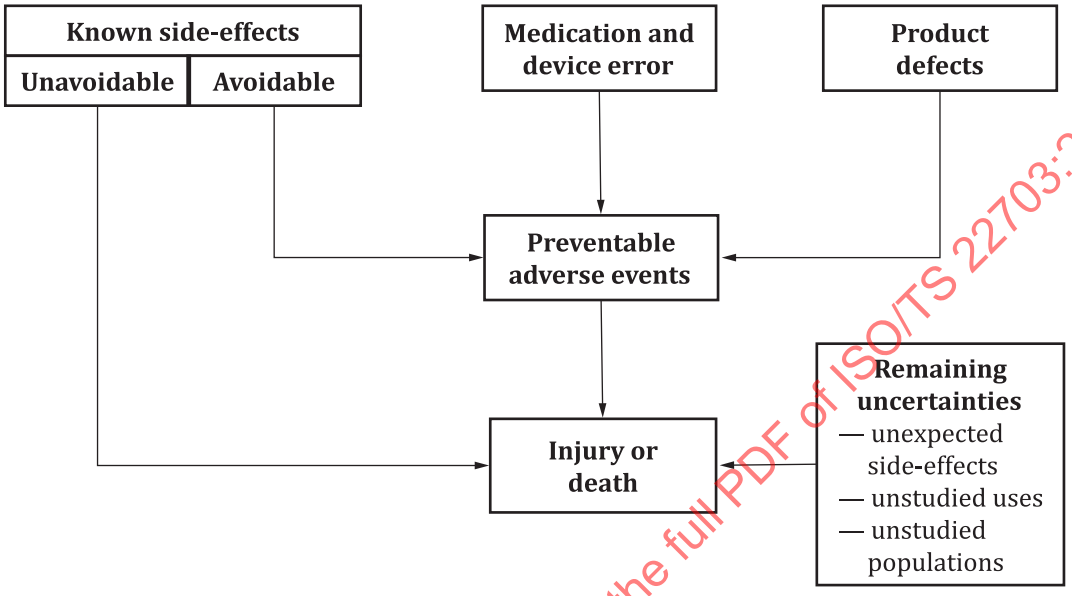


Figure 1 — Preventing ADRs[13]

A knowledge base can be the basis for detecting potential drug-related problems in a specific patient considering his or her clinical conditions (e.g. age, sex, concurrent medical diagnosis and medication, drug allergy history).

It is not within the scope of this document to create knowledge bases or gather patient clinical information. Rather, this document defines the requirements for selecting potential medication problem types for safety alerts based on the available knowledge, guides the method for how to find the conflicts between the predetermined thresholds (or standards) and prescription information (to be prescribed, dispensed or administered) based on specific patient clinical information and creates the signals to be alerted to healthcare providers in computerized health information system shown in Figure 2.

Although the rule-based knowledge base described in ISO/TS 22756 can contain a broader spectrum of rules for medication safety alerts than the scope of this document, this document focuses on the potential medication problem types which are more commonly selected in clinical settings to prevent or minimize drug-related problems and safety risks.

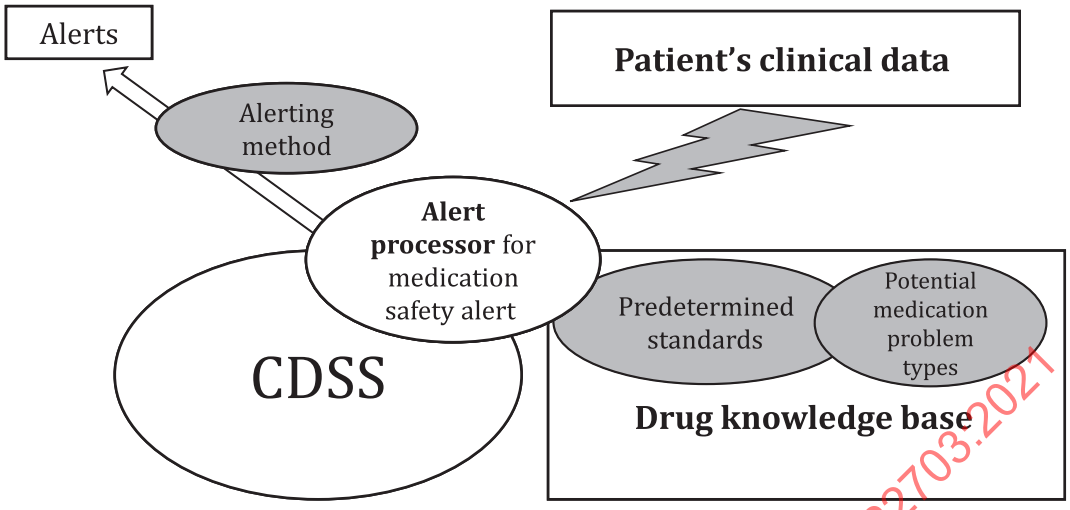


Figure 2 — Conceptual model for medication safety alert

5.2 Potential medication problem types for medication safety alerts

5.2.1 General

In principle, all potential safety risks of medication use fall into the scope of a medication safety alert system. However, the findings of potential safety risks for a specific patient can vary depending on the availability of data (e.g. patient clinical status, active problems, medication history, medication adverse event history), system capabilities (e.g. CDSS screening capabilities) and the information available in the associated drug knowledge base.

Ideally, the medication safety alert system should include as many of the potential problem types in this document as possible. However, the actual problem types implemented are determined by healthcare organizations in compliance with regional jurisdictions, pertinent regulations and guidelines for safe use of medication, while considering the available drug knowledge base and screening capability of the system.

5.2.2 Selection of potential medication problem types

There is no internationally agreed standard for selecting potential medication problem types for safety alerts. However, some national or regional jurisdictions have established requirements for medication safety alerts in the form of prospective and/or retrospective drug utilization review (DUR).

In the USA, the National Committee for Quality Assurance (NCQA), Centers for Medicare & Medicaid Services (CMS) and many other government agencies mandate that drug reviews be performed to ensure appropriate drug therapy. Specifically, the Omnibus Budget Reconciliation Act of 1990 (OBRA 90)[14] mandates that pharmacists conduct prospective and retrospective medication reviews whenever an outpatient prescription is dispensed to a Medicaid recipient. In US federal regulations, the following potential medication problem types for prospective DUR are specified for medication safety alerts when pharmacists are dispensing medication to patients in the community:

a) **Therapeutic duplication –** the prescribing and dispensing of two or more drugs from the same therapeutic class such that the combined daily dose puts the recipient at risk of an adverse medical result or incurs additional programme costs without additional therapeutic benefit.

b) **Drug–disease contraindication –** the potential for, or the occurrence of:

   1) an undesirable alteration of the therapeutic effect of a given drug because of the presence, in the patient for whom it is prescribed, of a disease condition; or

2) an adverse effect of the drug on the patient's disease condition.

c) **Adverse DDI –** the potential for, or occurrence of, a clinically significant adverse medical effect as a result of the recipient using two or more drugs together.

d) **Incorrect drug dosage –** the dosage lies outside the daily dosage specified in predetermined standards as necessary to achieve therapeutic benefit. Daily dosage is the strength multiplied by the quantity dispensed divided by day's supply.

e) **Incorrect duration of drug treatment –** the number of days of administered therapy exceeds or falls short of the recommendations contained in the predetermined standards.

f) **Drug–allergy interactions –** the potential for, or the occurrence of, an allergic reaction as a result of drug therapy.

g) **Clinical abuse or misuse –** the occurrence of situations referred to in the definitions of abuse, gross overuse, overutilization and underutilization, and incorrect dosage and duration.

To support this federal requirement for prospective DUR programmes, several drug knowledge bases have been developed and integrated in pharmacy software in the form of CDSSs and further integrated in health information systems (EHR) for hospitals in connection with the CPOE system.

In the Republic of Korea, the national authority (Ministry of Health and Welfare Affairs) mandates a prospective DUR programme similar to the prospective DUR programme in the USA when reimbursing pharmacy benefit costs to healthcare providers in both community pharmacies and health institutions. The potential medication problem types for prospective DUR are relatively fewer than those in the USA because of limited information resources for potential medication problem types and different definitions for predetermined standards. There are some additional types used for medication safety alerts (drug–age and drug–pregnancy contraindications).

In other countries it is possible that there are regional or national requirements for the potential medication problem types for medication safety alerts.

ISO/HL7 10781 should be referenced when choosing potential medication problem types. This document lists the functional requirements for managing medication orders including the following care provision domains and required supports for medication alerts:

1) Medication interaction and allergy checking

   — Determine and present the presence of interactions between medication ordered and medication already on the current medication list, true allergies on the current allergy list.

   — Determine and present the presence of contraindications between medication ordered and patient health condition and characteristics (e.g. gender, age, weight, smoking status, pregnancy status, renal function).

2) Patient-specific medication dosing and warning

   — Determine and render contraindications to the ordered dosage range (e.g. pregnancy, breast-feeding or occupational risks, hepatic or renal insufficiency).

3) Medication order efficiencies

   — Present a medication compendia or formulary content (e.g. drug, dose, route and SIG) to facilitate the selection of the medication to be ordered.

Though the potential medication problem types for medication safety alerts will be broader or narrower depending on the availability of knowledge bases, the frequently used types for medication safety alerts in connection with CDSS include:

— therapeutic duplication

— drug–disease contraindication

— adverse DDI

— incorrect drug dosage

— incorrect duration of drug treatment

— drug–allergy interactions

— drug–age contraindication

— drug–pregnancy contraindication

To enable medication safety alert systems in conjunction with an EHR, the potential medication problem types should be derived from the information and rules in the knowledge base (hereafter referred to as rule-based knowledge base systems), presumably abstracted from most trusted drug information resources. In other words, the availability of trigger rules based on the selected drug knowledge base will limit the medication alert types that can be chosen.

Considering these limits on the potential medication problem types used for medication safety alert internationally and the specific needs of healthcare organizations and specialities (e.g. intensive care units or paediatricians might want to cover fewer types, but more in-depth and specific types), the following factors need to be taken into account in selecting the potential medication problem types:

— availability (accessibility) of patient clinical information (patient health records);

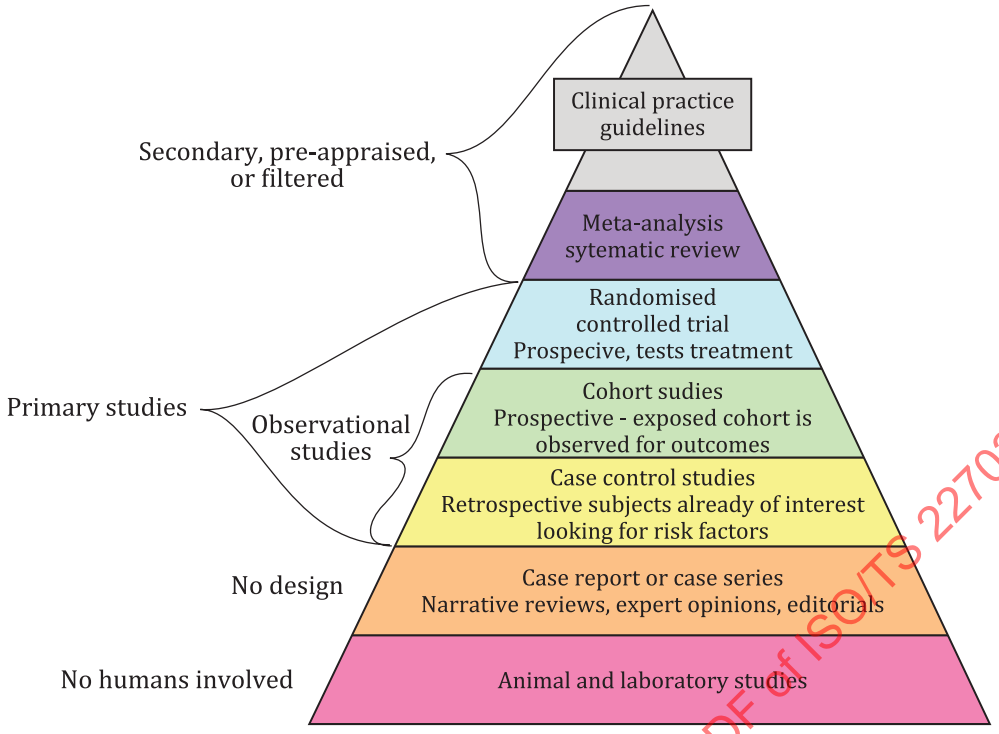
— capacity (hardware or software) of the health information system;

— formulary and formulary systems (national or institutional);

— drug knowledge base (digitized) availability for predetermined standards;

— decision support capability of health information systems.

In addition, the quality of knowledge base is an important factor in selecting potential medication problem types. In the era of evidence-based medical practice, the strength of the scientific evidence for each knowledge base will be based on the hierarchy of evidence level shown in Figure 3.



SOURCE "Research design and evidence" by CFCF, available at https://commons.wikimedia.org/wiki/File:Research_design_and_evidence.svg. Used with permission from Wikimedia Commons.

Figure 3 — The hierarchy of research designs and levels of scientific evidence

In choosing a knowledge base for CDSS, the quality or strength of scientific evidence is also important. There is general consensus among healthcare professions that the evidence-based practice is the best choice in pursuing the best possible outcomes in caring for patients.

Regarding the quality of knowledge bases, the US Code of Federal Regulations (CFR) 42§456.702 explicitly describes the requirement of the information resource for knowledge base (specifically predetermined standards) as described in 5.2.4.

5.2.3 Other potential medication problem types

Potential medication safety risks should be prospectively identified and minimized or prevented across a broad scope of alert types. Hence, the potential medication problem types shall not be limited to the ones suggested in this document.

The types listed in 5.2.2 are purely clinical context focused detectable safety risks from the perspective of prescribers and dispensers. However, the larger healthcare organizations (hospitals) may include more types from the perspectives of prescriber and persons responsible for drug administration, while also considering patient specific clinical data (e.g. clinical laboratory data, vital signs, blood drug concentration data, nutrition) and drug use policies (or guidelines) (e.g. antibiotics use guideline, diagnosis and drug choice matching, drug and laboratory test interaction, drug and food interaction, injectable drug incompatibility).

Also, though not directly related to patient safety, other administrative or managerial requirements can be added to the system to improve the outcomes of patient care if system capacity allows.

5.2.4 Predetermined standards for potential medication problem types

Once the potential medication problem types for medication safety alert are chosen for organizational or national level, the predetermined triggering standards (safe range of dose, for example, maximum and minimum dosage range for specific indication) for each type should be decided.

If there is no appropriate knowledge base in the region, ISO/TS 22756:2020, Clause 7, can be referenced to assess potential sources for a rule-based knowledge base.

The predetermined trigger standards can be abstracted from the available information resources (specifically rule-based knowledge bases defined in ISO/TS 22756 or defined by the regional or institutional authorities).

One example for defining predetermined trigger standards for prospective DUR programmes is described in USA federal regulations (requirements for predetermined standards) (see Annex A).

In conclusion, if there are no specific regulatory requirements for the predetermined standards in the region (or country), choose a knowledge base that conforms with ISO/TS 22756.

In some countries, an organized drug (pharmacy) and therapeutics committee (DTC) has been shown to be effective in safeguarding and promoting efficient and rational use of medicines[16] by, for example:

— establishing documented rules and policies for all aspects of drug management, including the selection of formulary list medicines and agreement of treatment protocols;

— conducting continuing education, audit and feedback, DUR and monitoring of adverse drug reactions and medication errors.

In such cases, national or institutional authorities (such as DTC) shall be the best bodies responsible for choosing the potential medication problem types for safety alerts and defining the scope of rule-based knowledge bases (predetermined alert trigger standards) in developing and implementing medication safety alert systems at organizational or national level.

5.3 Data sources of potential medication problem types and predetermined standards

5.3.1 Evidence-based resources

Once the types of medication safety alerts have been reviewed and selected, the appropriate drug knowledge base (rule-based knowledge base for CDSS) should be examined to establish the predetermined alert trigger standards that will be used for prospective screening and detecting the potential safety risks of new medication orders by the specific algorithms of the CDSS.

For developing or selecting the drug knowledge database, the concept of evidence-based resources may be safest and best since the context of safety alerts should be objectively and clinically proven by quality evidence.

A typical example of defining evidence-based resources for medication safety alert is found in the USA federal regulation for the prospective DUR programme regarding the predetermined standards for DUR as described in 5.2.4. One example of information resources in compliance with this federal regulation requirement is American Hospital Formulary Service (AHFS) - Drug Information which is a compilation of peer-reviewed drug monographs for the approved medicinal products in US markets.

Thus, the requirements for predetermined standards as described in 5.2.4 are recommended as the knowledge base for developing predetermined standards for the chosen types for medication safety alerts.

Investigational medicines in clinical trials will not in general have sufficient information in the CDSS for medication safety alerts due to the unavailability of evidence-based resources on potential medication problem types. Therefore, investigational medicines are not included in the scope of this document.

5.3.2 Other resources

Some countries other than the USA have or own the drug knowledge base in the scope defined in 5.3.1. As an alternative, many countries who do not have well-developed knowledge bases use the package insert (or labelling) information as well as obtainable drug information bases available in the region.

Drug knowledge bases meeting the definition of 5.3.1 are, almost universally, commercial products. However, the drug knowledge bases utilize public information resources held by government agencies or other non-commercial entities. The information in these resources can contain labelling information, drug naming, medication content information and other information useful for medication alert systems.

If the country employs ISO IDMP (identification of medicinal products) standards (see ISO 11238, ISO 11239, ISO 11240, ISO 11615, ISO 11616), then a medicinal product dictionary (MPD) (see ISO/TS 19256) or product labelling [structured product labelling (SPL)][15] or both are likely to be available. ISO/TS 22756 provides guidance on how IDMP and other resources (as the sources for evidence) can be utilized in the development of CDSS in such cases.

Thus, the concepts of drug knowledge resources for CDSS defined in ISO/TS 22756 should be considered along with the requirements in this document.

5.3.3 Patient data sources

To produce safety alerts, CDSS (with algorithms) shall be able to apply the predetermined alert trigger standards against specific patient's clinical data.

To meet all the potential medication problem types for the required medication safety alert, an accurate and comprehensive electronic patient profile in connection with EHR or PEHR should be available.

If the EHR conforms with ISO/HL7 10781, CDSS can be easily connected to patient clinical data.

If there is no standardized requirement for patient clinical data, ISO 27269 is a possible alternative. This standard provides a specification of a patient summary from which derived profiles are implementable and the core data set includes the following information:

— age (for drug–age alert);

— gender (for drug–gender alert);

— allergy/intolerance-agents (for drug–allergy alert);

— co-medication (for therapeutic duplication and drug interaction alert);

— diagnosis (for drug–disease alert);

— pregnancy (for drug–pregnancy alert);

— laboratory values (for drug–clinical laboratory test interaction).

An organization that develops medication safety alert systems based on a knowledge base shall consider and decide which kind of patient data will be included in the rules, in cases where rules are developed that include patient data. The choice for including more or less variables leads to different kinds of rules: sophisticated ones with sophisticated patient data or less detailed rules with less patient data.

Beside the information mentioned above, other information can be relevant to include in the knowledge rules, such as the severity of the disease, pharmacogenetic data or racial data. The organization that develops a knowledge base shall decide which of these kinds of data will be included in the knowledge base.

5.4 Alert processor

To have the CDSS function to generate the safety alerts, a core engine in the CDSS needs to be connected to the rule-based knowledge base (which contains predetermined alert trigger standards for corresponding potential medication problem type) and concurrently to patient clinical information.

Even if the predetermined standards for potential medication problem types and patient's clinical data are available, there is no other way to produce alert signals without the appropriate processor with algorithms (hereafter alert processor) which are designed to screen each clinical and newly ordered prescription data against the predetermined standards of each problem type.

To have this alert processor actionable, all data elements for drug products shall be digitized and coded with a link to related medication problem types as depicted in Figure 4.

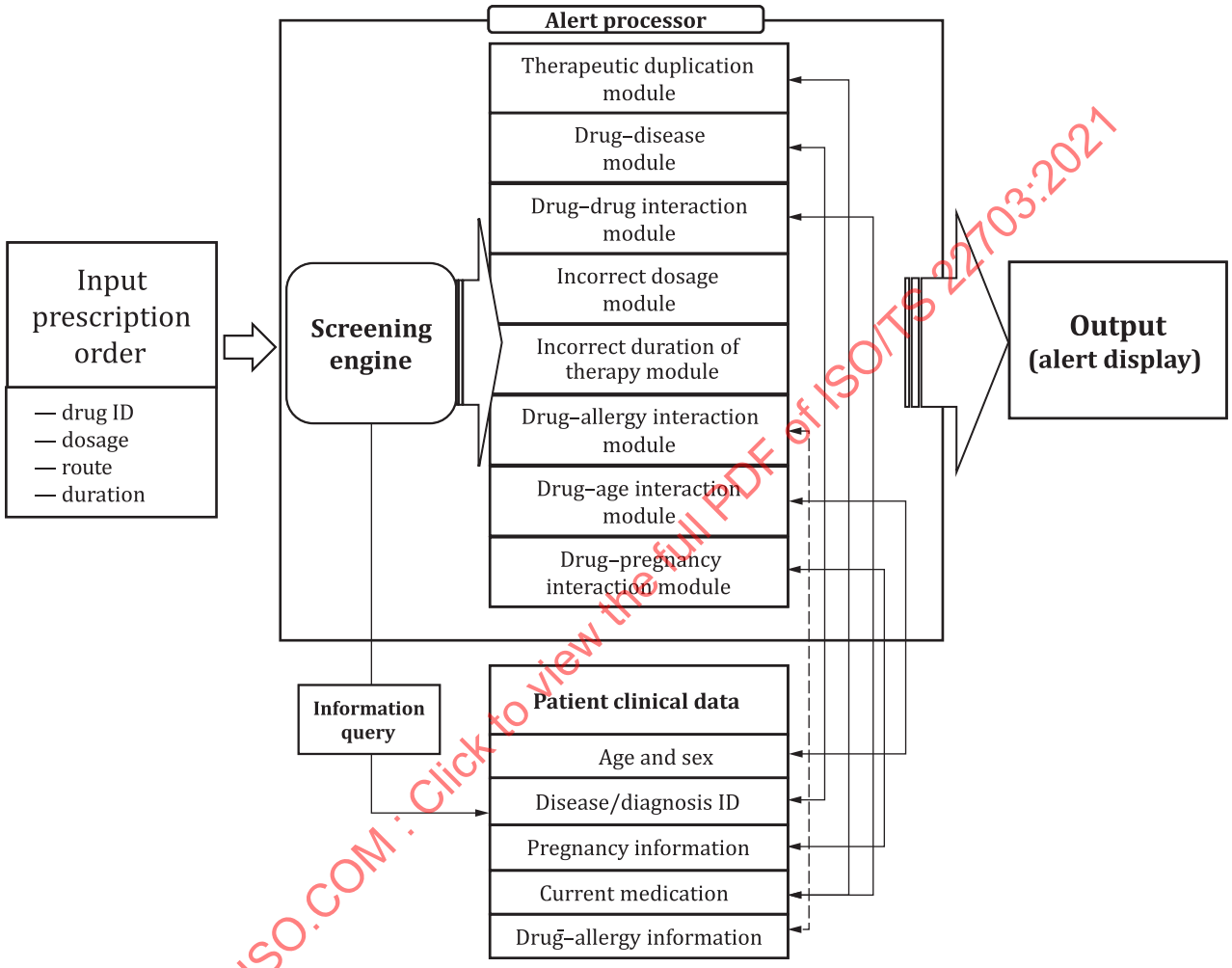


Figure 4 — Conceptual diagram of alert processor

The alert processor in the CDSS needs to connect the patient data to the data elements in the rules or information from the knowledge base and process the rules if new patient data are registered which are relevant to the rules that are applicable for a patient. The result should be shown to the healthcare providers in a way that fits into their workflows (e.g. no popup, but a list at the end of the day). The CDSS also needs to have the functionality to reduce alert fatigue by allowing the suppression of alerts after the users have seen it and acknowledged. In addition, it should be possible to suppress specific alerts for nominated healthcare providers or groups.

Due to its complexity and sophistication, as well as the huge amount of labour requirement in developing and updating the digitized and coded data elements for drug products, the alert processor is often a proprietary product in the form of content software.

Thus, the requirements for alert processor development are not included in the scope of this document. However, IEC 82304-1 should be followed when developing such products to ensure that adequate risk mitigation is achieved. This document focuses on the alerting guidelines (methods) which alert processors should follow.

5.5 Alerting guidelines (methods)

5.5.1 General

There is no shared consensus on terms used in medication safety alerts. For example, there are no agreed-upon, standardized terms designating clinical significance of alerts (or severity levels), alert schema and option for alert signalling (interruptive or non-interruptive).

In alerting potential DDIs, some alerting systems use a three-tier severity level scheme (i.e. high, moderate, low) while others use a two-tier scheme (i.e. critical, significant), numbers (i.e. level 1, level 2, level 3) or severity levels with descriptive explanation attached (i.e. high severity with strong evidence, high severity with moderate evidence, moderate severity with strong evidence).

Consensus on terms is required to enable interoperability between alerting systems used in health organizations, which have so far been using different terminologies in medication safety alerts.

5.5.2 Severity or safety risk grading

A grading or classifying of the severity or clinical significance of medication-related problems is required when implementing CDSS for medication safety alerts. This content shall be part of the rule-based knowledge base for CDSS as described in ISO/TS 22756.

If a knowledge base with severity or significance grading is available, the CDSS developer should follow the implementation guidelines of the knowledge base vendor and create only the correct alerts and prevent unnecessary alerts according to the institutional needs.

In principle, the users of CDSS shall be alerted to all the medication problem types to prevent any potential ADRs.

For the chosen potential medication problem types for medication safety alert in 5.2.1, all the outputs produced by the alert processor shall be shown to the users. However, since it is known that too many (frequent) alerts can lead to inappropriate overrides, clinician refusal to use the EHR medication management system or unanticipated outcomes (increased number of errors or adverse events), a severity or safety risk grading system can be useful to minimize alert fatigue[17].

Depending on the characteristics of the potential medication problem types, the grading requirements can be different, as described in Table 1.

Table 1 — Safety risk grading requirements for potential medication problem types

No.	Criteria	Safety risk grading	Predetermined standards
1	Therapeutic duplication	No	No ingredient and therapeutic class duplication allowed
2	Drug–disease contraindication	Yes	Absolute and relative contraindication
3	Adverse DDI	Yes	Contraindicated, provisionally contraindicated, conditional, minimal safety risk and no intervention
4	Incorrect drug dosage	No	Minimum and maximum daily dose
5	Incorrect duration of drug treatment	No	Correct duration range (days)
6	Drug–allergy interactions	No	Same ingredient and drug with cross-sensitivity
7	Drug–age interactions	Yes	Contraindication and precaution
8	Drug–pregnancy contraindication	No	Contraindication

Severity grading or classification has been mostly applied to alerting DDIs using various grading or classifying schemes.

In grading (or classifying) drug interactions, the operational classification (ORCA) system has been proposed by the Drug Interaction Foundation (DIF) with input from an international group of experts and is shown in Table 2[18].

Table 2 — ORCA system for classifying drugs interactions

Class	Description
1. Contraindicated	No situations have been identified where the benefit of the combination outweighs the risk.
2. Provisionally contraindicated	The combination increases the risk of adverse effects. Avoid concurrent use unless interaction is desired or no alternative is available. If the combination is used, increased monitoring may be necessary.
3. Conditional	Risk may be increased, depending on the clinical situation. Assess risk and take action as needed.
4. Minimal risk	Risk of adverse outcome appears small. No special precautions appear necessary.
5. No interaction	Evidence suggests that drugs do not interact.

These requirements for severity grading will be within the scope of a knowledge base for CDSS and thus ISO/TS 22756 shall be referenced in developing medication safety alert systems.

Alert fatigue can stem from a combination of EHR and drug knowledge base factors including inflexibility, inability to provide relevant, clear, sufficient and up-to-date information, disruption of workflow, failure to deliver alerts at the right time based on severity and urgency of conditions, and failure to tailor rules to user preferences[22].

Thus, the alert processor (CDSS) shall be patient-specific and use interruptive or non-interruptive alerts. In this case, non-interruptive alerts make the notification available for resolution at a time convenient to clinicians while interruptive alerts provide real-time warnings and require users to take action to respond to the alert[21].

In addition, one of the biggest arguments against eliminating or even decreasing the number of alerts to minimize alert fatigue is fear of liability among EHR vendors, and healthcare organizations if patients are harmed.

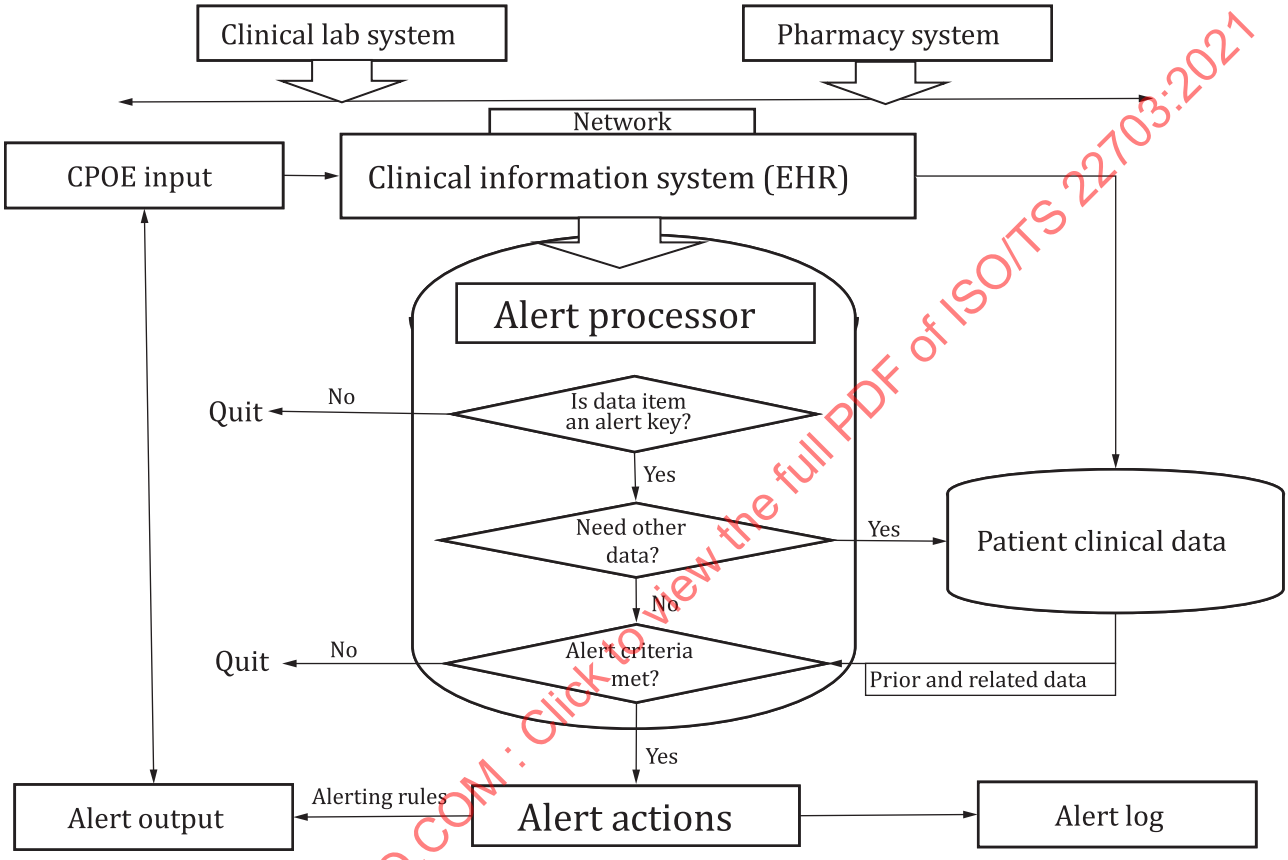
To minimize liability, the alert systems shall use the rules with only the most important warnings or tailor alerts to a specific clinical environment, user groups or populations of patients. When choosing

a knowledge base with the optional criteria for severity grading, the use of a flexibility configuration system (see Annex B) can be an alternative way to avoid or minimize alert fatigue.

In conclusion, it is more important to focus on overall alert system design rather than solely focus on severity or safety risk grading to eliminate or minimize the number of alerts.

5.5.3 Alert schema

Medication safety alert system shall be placed in health information systems as one component (alert processor) of EHR as depicted in Figure 5.



NOTE Figure modified from Reference [19].

Figure 5 — Alert detection system

5.5.4 Display of medication safety alert

A research report investigating the variation in DDI alerts across institutions and EHRs in the USA includes recommendations for the methods to be used to display DDI (see Annex C).[20] In this report, the table contains two types of useful information which can be applied to other potential medication problem types:

a) Information related to 5.5.2, namely about what to do to diminish unnecessary alerts (e.g. institutional flexibility, grading)

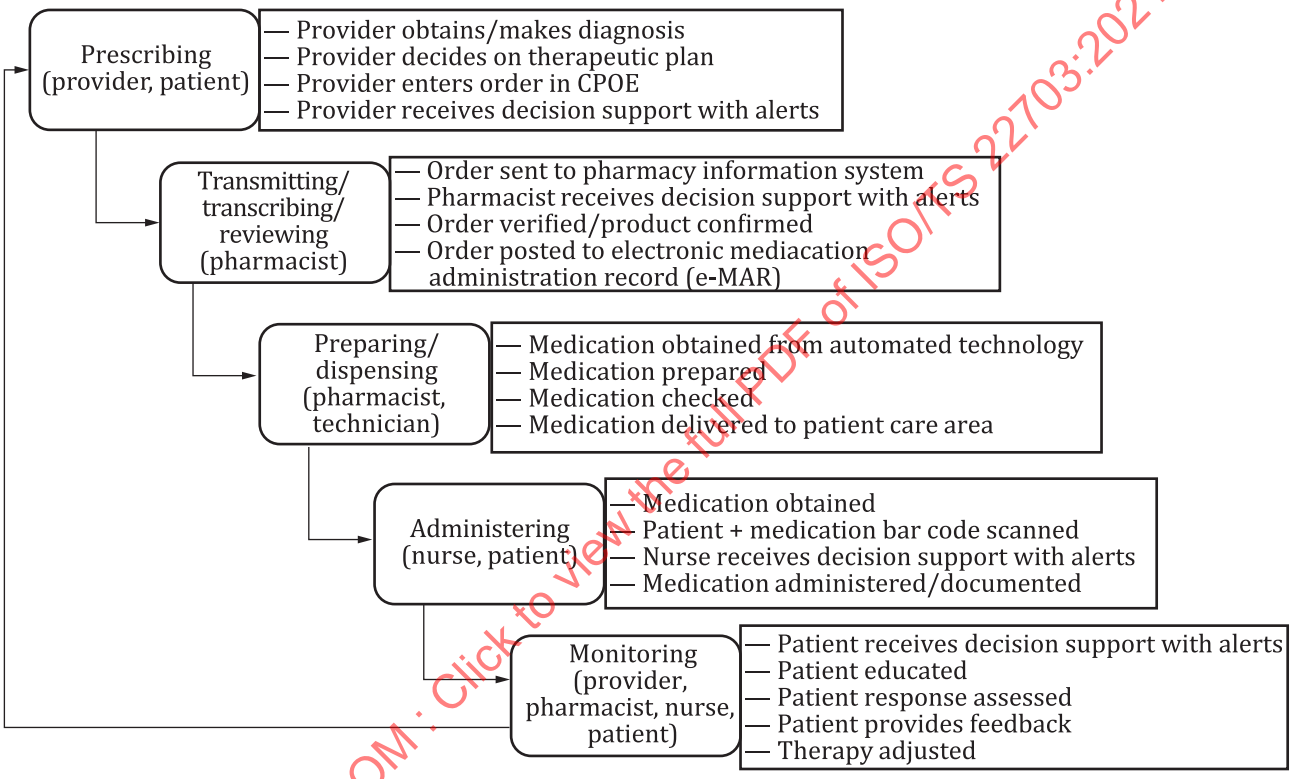
b) Information that is purely about what to show once there is an alert (e.g. colours, drug involved)

If CDSS is based on a knowledge base conforming with ISO/TS 22756, any content related to safety alert display shall be referenced first.

The alerts shall be displayed individually on a real-time basis whenever the prescribing information is selected or input into the CPOE system or displayed as the alerts list with decision support information with (or without) a monograph (e.g. summarized information for drugs involved, seriousness, clinical consequences, mechanism of action, recommended action, evidences) for the displayed alerts immediately after prescriber finalizes the prescribing information (see Annex D).

5.5.5 Alert receivers

A safe medication use process is built on interdisciplinary interactions and cooperation to ensure that patients receive the best possible care. CDSS with an alert processor applies to all clinicians on the care team: prescribers, pharmacists, nurses, patients and others (Figure 6).



NOTE Figure modified from Reference [20].

Figure 6 — Schematic of inter-professional decision support to facilitate patient safety (hospital setting)

For non-prescribing clinicians, safety alerts can be deployed as a second check to help ensure that patients receiving drugs are being monitored or assessed. Patient care and safety are best achieved when all members of the team have knowledge of what other members are doing.

In most clinical settings, the alerts can be given to healthcare providers who are prescribing, dispensing or administering medication as depicted in Figure 6. In some circumstances, the alerts can be given to the patients who are using a self-managed information system that is directly connected to an EHR.

In this document, only healthcare professionals who hold the rights to prescribe, dispense or administer the prescription drugs in the settings where the alerts are generated in connection with an EHR are considered as alert receivers (or users). The healthcare professionals who are alert receivers fulfil the following roles:

— Prescriber: in most countries, the prescriber will be the physician who is directly caring for the patient. However, the prescriber can be other healthcare providers, including pharmacists and nurses, who have the right to prescribe medication.

— Dispenser (pharmacist): in most countries, the dispenser will be the pharmacist who is caring for the patient.

— Administering persons (nurses): in most countries, registered nurses will be responsible for administering the dispensed drugs and keeping medication administration records in hospital or clinical settings.

5.5.6 Alert timings

Without exception, the alert shall be given at the right time which is usually and preferably ordering, dispensing or administering. If the chosen knowledge base for CDSS indicates the moment of alerting, the alert timings shall follow that guidance. If not, the alert messages or signals shall be displayed at least at the points of the followings actions:

— immediately after the prescriber completes a medication order in a CPOE system;

— immediately before a dispenser takes action regarding actual dispensing (preparation process for administering the prescribed medication);

— immediately before a nurse or patient (if the patient is directly connected with EHR via apps in outpatient settings) takes action regarding actual administration of the dispensed medication.

5.5.7 Alert interventions

Alerts may be accompanied with corresponding informative data displaying the reasons for each alert and, if appropriate, corrective actions to be taken by healthcare providers.

When a clinician uses a CPOE system connected with an alert processor, he or she shall be able to take immediate action to resolve the encountered problem(s) by changing prescription information.

Secondary checkers (pharmacists and nurses) should take interventions to solve the problems by communicating to prescribers or patients during drug use review (medication use evaluation) immediately before dispensing or administering the prescribed medication.

A prescriber's own corrective actions together with effective interventions by secondary checkers can increase the effectiveness of medication safety screening by allowing the clinician's preference (high severity level alerts only to prescribers and other remaining alerts to pharmacists or nurses) if well-designed standardized operating procedures (SOP) for medication safety are implemented in the institution (see ISO/HL7 10781).

The system shall render alerts and notifications when new medication is ordered as follows:

— The system shall provide the ability to edit a medication order by overriding the medication alert or warning and transmitting the updated medication order.

— The system shall provide the ability to capture reasons for overriding a medication alert or warning at the time of ordering.

— The system shall provide the ability to tag and render an indication that a provider has overridden a medication alert or warning.

5.5.8 Audit trail

The traceability of what has been alerted and which actions have been taken by the healthcare providers is critical, as it is for other actions in EHR environments viewed from technical safeguards of health information.

To maintain the traceability for the actions on medication safety alerts, organizations with an EHR system shall conform with ISO 27789 for implementing hardware, software and procedural mechanisms that record and examine activity in information systems that contain or use protected health information. Part of the audit trail shall be which alerts have been generated and when, which

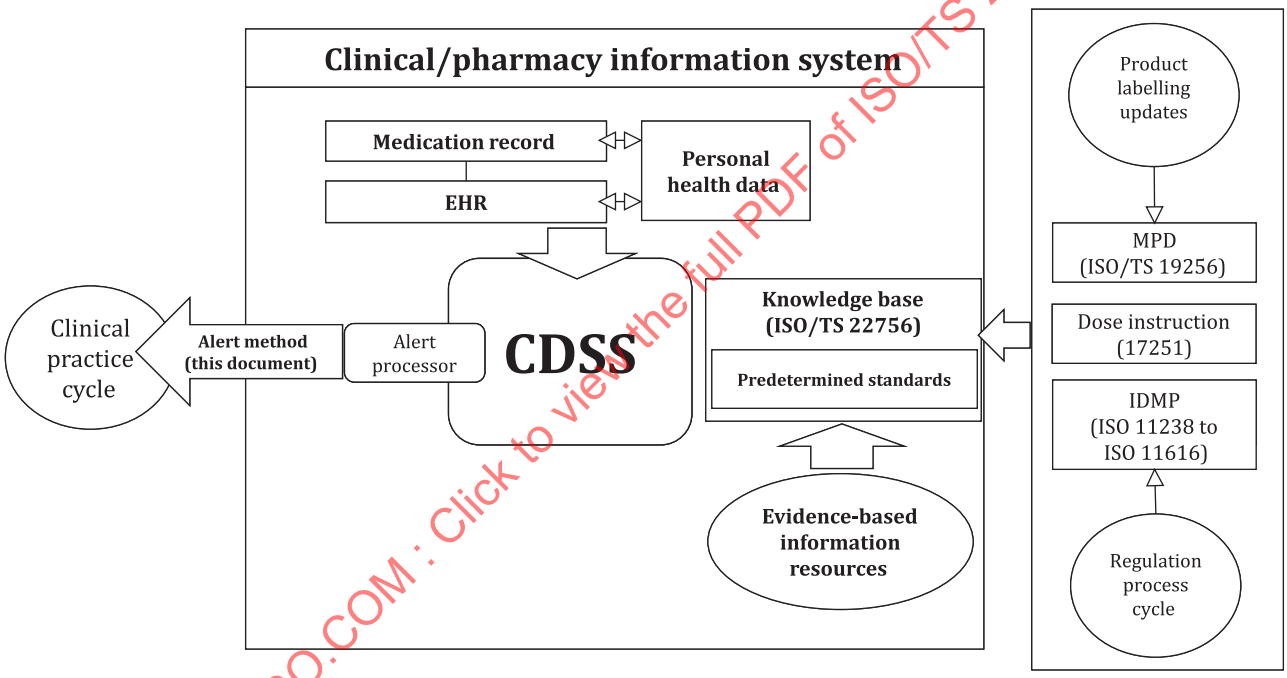
users the alert was shown to, the alert text that was displayed and what action (if any) was taken by the user as a consequence of the alert. In particular this shall include whether an alert was overridden and when alerts types are enabled or disabled by users.

5.6 Interfaces and relations

5.6.1 General

In digitized health information systems, medication safety alerts shall be generated when the alert processor screens the prescription order information and the predetermined standards of the selected potential medication problem types which will be abstracted and built from the knowledge bases, in consideration of patients' clinical and medication history information, which will be abstracted from the EHR or PEHR.

Medication safety alert system will be incorporated as one component of a CDSS in EHR or PEHR as shown in Figure 7.



NOTE Figure modified from ISO/TS 22756.

Figure 7 — Alert processor in relation to health/clinical/pharmacy information systems

5.6.2 Clinical information system

5.6.2.1 General

The medication safety alert system shall be integrated into the CDSS which is directly connected to the knowledge database and patient's clinical profile in a digital EHR with CPOE functionality as depicted in Figure 7.

5.6.2.2 Relation with a CDSS

The core part of a medication safety alert system will be the alert processor as one component of CDSS that is directly connected to the knowledge base and interfaces to the user's visual window.

Thus, this document is harmonized with ISO/TS 22756 in describing the requirements for the knowledge base for CDSS.

5.6.2.3 Relation with EHR

The medication safety alert system shall be directly connected to EHR or PEHR, which contains patient information (clinical and administrative).

ISO/HL7 10781 shall be referenced in developing a medication safety alert system to have a CDSS actionable from a patient's clinical data in the EHR.

ISO/TS 22756:2020, 6.9 to 6.11, which describe the rules for medication safety alerts, shall also be referenced in developing the system.

5.6.3 Pharmacy information system

For ambulatory (outpatient, community) patients, the prescribed medication is dispensed in community pharmacies. The pharmacy software in these pharmacies can have a medication safety alert system (alert processor), with alerts presented to the pharmacist.

The fundamental features and functions of medication safety alert systems (alert processors) in PEHRs are similar to those in other EHRs. There are advantages and disadvantages for medication safety alert systems in pharmacy software compared with those in other EHRs.

The advantages are as follows:

— A PEHR may have more complete medication history for each patient when a patient visits multiple medical clinics or hospitals (see ISO/TS 19293). In this situation, the alert processor in the PEHR provides better opportunities to identify therapeutic duplications and DDIs.

— A PEHR medication history may include non-prescription drugs. In this situation, the PEHR can have broader screening capability for DDIs.

— In some countries (e.g. USA, Republic of Korea) the PEHR can receive medication alerts from the DUR system of linked pharmacy benefit managers (PBM). In this situation, the efficiency of medication safety alerts can be greatly increased by stepwise safety checking by the associated DUR system (primary) and subsequently by the PBM DUR system (secondary) (see Figure 8).

— Where electronic prescribing (see ISO 17523) is available between prescribers and pharmacies, both the prescriber's EHR (CPOE) and the PEHR can benefit. Additional interoperability options between health institutions can greatly improve medication safety by sharing the PEHR medication records and clinical information from other EHRs.

The disadvantages are as follows:

— Important clinical information (diagnosis and clinical laboratory tests) for the patient cannot be available in the PEHR. In this situation, the alert processor cannot detect potential safety alerts, including drug–disease contraindications or drug–laboratory test interactions.

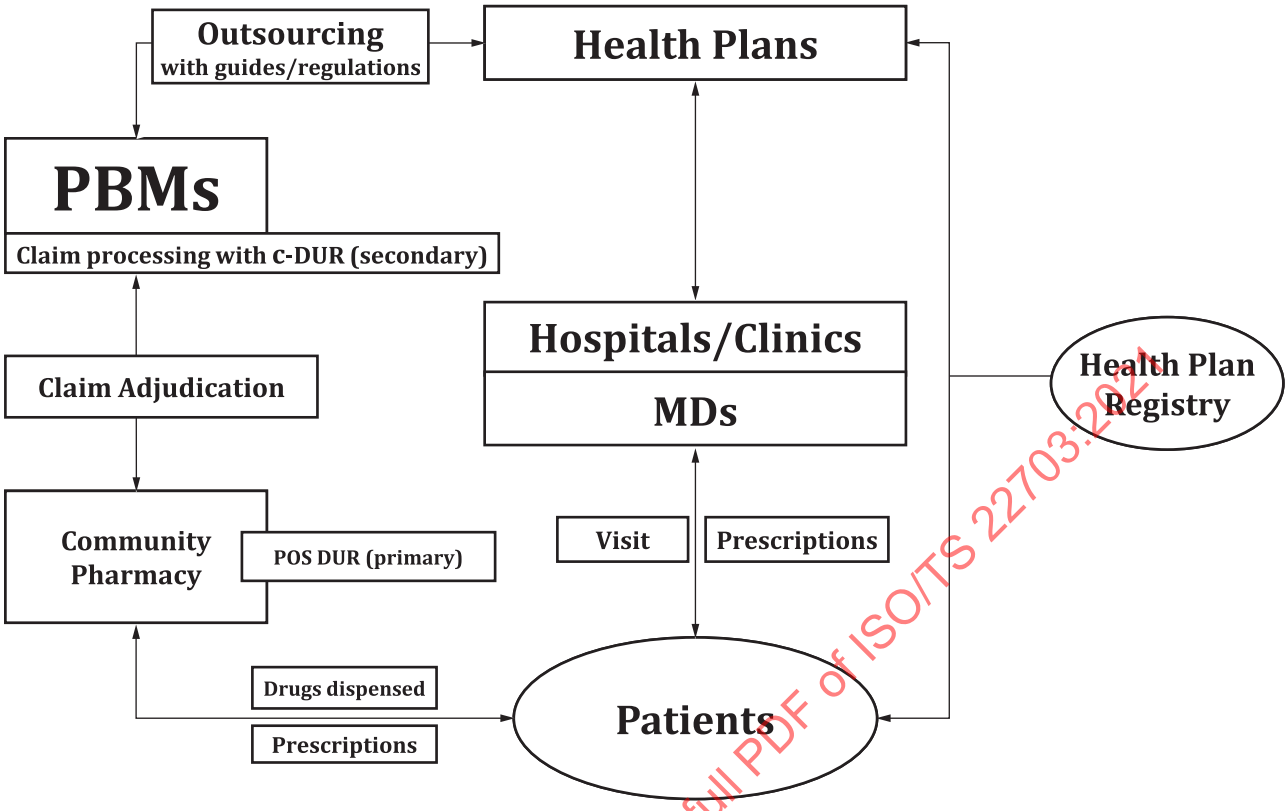


Figure 8 — Prospective DUR programme network for prescription drugs

5.6.4 Relation to international standards

As noted in 5.4, medication safety alert systems (alert processors) in CDSS require relational databases for potential medication problem types based on a drug knowledge base.

ISO/TS 22756 describes the requirements for a knowledge base for CDSS which can be the shared ground for developing a medication safety alert system.

The requirements for medication safety alerts specified by ISO/TS 22756 shall be followed.

In countries where IDMP standards (see ISO 11238, ISO 11239, ISO 11240, ISO 11615, ISO 11616) with MPD (see ISO/TS 19256) are fully implemented and include all the marketed drug products, the knowledge base for CDSS will be more easily developed and consequently utilized for building safety alert systems in the scope of this document.

6 Other recommendations

6.1 General

The development and implementation processes of medication safety alert systems include many complex stages before the system can be actually operated in clinical settings. All the processes shall conform with IEC 82304-1. Figure 9 provides additional guidance specific to the alert processor module.

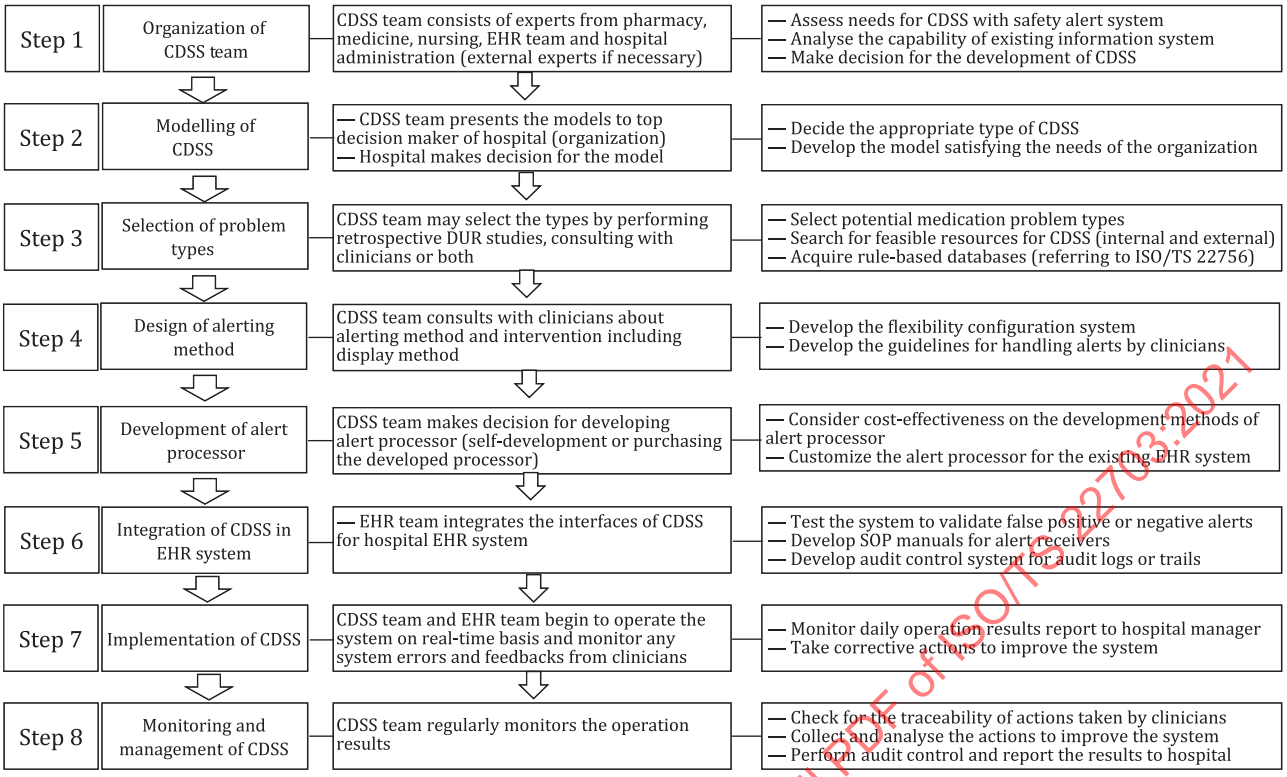


Figure 9 — Developing and implementing process of medication safety alert systems

6.2 Pre-development steps

In Figure 9, step 1 to step 4 can be considered as pre-development steps. As described in 5.2.4, the organization of a CDSS team can be established by an institutional authority (such as DTC). Once the CDSS team has been organized, the team shall collect and analyse all the available resources for developing the CDSS with a safety alert system and develop the conceptual model for the system based on the required and available information and resources.

After choosing the type of CDSS, the team shall select the potential medication problem types to be included, considering regional regulations and the needs of potential users within the organization as well as design alerting methods following the requirements of this document.

6.3 Development steps

In Figure 9, steps 5 and 6 describe the actual development of the CDSS with a safety alert system to be integrated into the existing EHR system.

To develop the alert processor, the CDSS team can consider either self-development with internal resources or the use of available resources from the market place. In deciding the development method, a cost-benefit study should be performed because of the complexity and extensive resource requirements (e.g. human resources, time, information databases) of the system development as described in 5.4.

Once the alert processor has been developed it should be integrated into the existing EHR system. Though this system integration appears to be purely technical, the CDSS team should be involved in the whole process by providing subject matter experts to the system integration team on a continual basis.

6.4 Implementation step

The implementation step includes a test trial period with a separate system and then a live operation period with the existing EHR environment. During the live operation period, the CDSS team shall closely monitor the operation results in order to take corrective actions for any system errors.

6.5 Monitoring and management of the system

Even though the implementation of the system has been successfully completed, the system cannot be perfect and thus a continuous quality improvement programme is needed including collecting and analysing the outputs and actions to improve the system efficiency and maintain the traceability of actions taken by users for audit control.

Annex A
(informative)

Example of definition and requirement of predetermined standards[1)]

Definition: Predetermined standards means criteria and standards that have been established in accordance with the requirements of CFR 42§456.703 (drug use review programme).

Requirement: The predetermined standards used in the DUR programme shall meet the following requirements (CFR 42§456.703):

1) The source materials for their development are consistent with peer-reviewed medical literature (that is, scientific, medical,and pharmaceutical publications in which original manuscripts are published only after having been critically reviewed by unbiased independent experts) and the following compendia: i) American Hospital Formulary Service Drug Information; ii) United States Pharmacopeia-Drug Information; iii) American Medical Association Drug Evaluations.

2) Differences between source materials were resolved by physicians and pharmacists developing consensus solutions. The consensus process means the reliance, by the criteria developers, on the expertise of physicians and pharmacists to evaluate differences in criteria source materials and to come to agreement on how differences should be resolved.

3) They are non-proprietary and readily available to providers of services. Systems and algorithms using the predetermined standards may remain proprietary.

4) They are clinically-based and scientifically valid.

5) The review based on clinical criteria uses predetermined standards to determine the population at risk of a clinically significant adverse medical result and applies standards, appropriate to this population, across providers and patients to determine the provider outliers whose prescribing, dispensing or consumption practices may not conform to accepted standards of care. Various statistical measures (including mean, range or other measures at the discretion of the State) may be applied to these data. Standards may be considered in deciding if an in-depth review is needed to determine whether to intervene once the potential therapeutic problems have been identified through the use of clinical criteria.

6) They have been tested against claims data prior to adoption in order to validate the level of possibly significant therapeutic problems without undue levels of false positives.

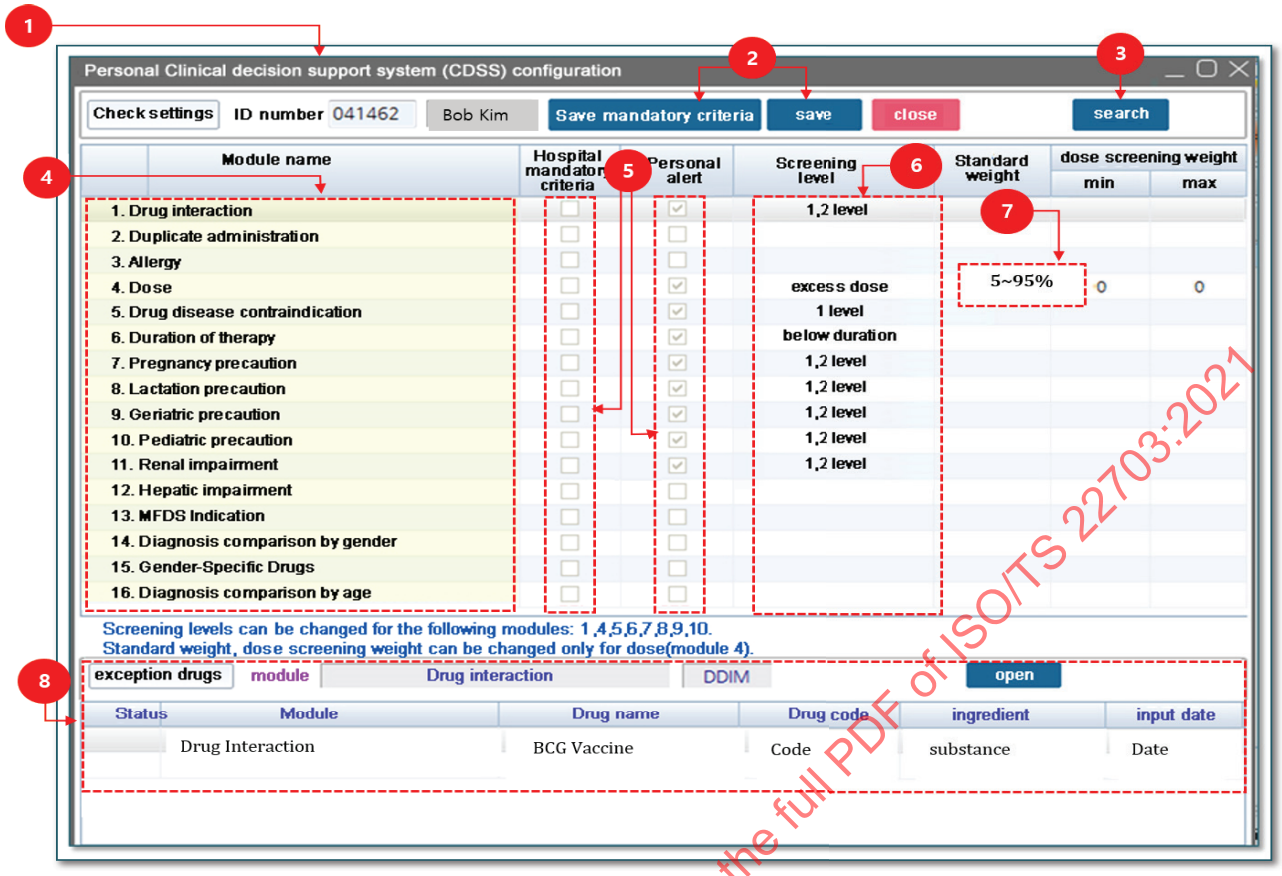
7) The predetermined standards for prospective and retrospective DUR are compatible.

8) They are subjected to ongoing evaluation and modification either as a result of actions by their developer or as a result of recommendations by the DUR Board.

1) Source: US CFR 42§456.702–703, available at https://www.govinfo.gov/content/pkg/CFR-2011-title42-vol4/pdf/CFR-2011-title42-vol4-sec456-702.pdf.

Annex B
(informative)

A flexibility configuration setting screen shot of a CDSS system (a case in Korea)



Key

1 The CDSS configuration settings page lists the current settings of each screening module.

2 The settings can be saved as mandatory or default. Default settings can be modified by general users (non-super users). Mandatory settings are always used for all users and cannot be overridden by general users. Only super users can modify the mandatory settings.

3 Search button: super users can enter a general user's ID number and click search button to browse each general user's personal account settings.

4 The list of CDSS modules integrated into the EHR is displayed.

5 Checkbox: the left checkbox is for assigning mandatory settings which can only be modified by super users. The right checkbox is for assigning default settings which can be modified and customized by each user.

6 The severity levels of alerts that are to be visible to the user can be assigned for each selected CDSS module.

7 Ideal body weight table is used to estimate a patient's weight for drug dosing when the exact weight is unknown.

8 To minimize nuisance, a list of excluded medication can be registered for each CDSS module (e.g. BCG vaccine registered as excluded medication in drug interaction module will be excluded from drug interaction review).

NOTE While the default configuration settings are appropriate for most cases, users are able to modify and personalize the settings from the CDSS configuration settings page which contains the above key references.

Figure B.1 — Example of a flexibility configuration system

Annex C
(informative)

Recommendations for DDI alert display

1. What information to display in DDI alerts?		
Requirement	**Recommendation**	**Description or example**
Drugs involved	Interacting drugs should be clearly identified in a dialogue box	— Critical information should be present within an alert, including names of the interacting drugs. Specifying interacting agents should make it immediately clear for what the DDI alert is being displayed. — Inappropriate listing of DDIs by pharmacologic or therapeutic class can lead to the clinician incorrectly assuming that the DDI applies to the entire class of medication. — This does not preclude mentioning pharmacologic or therapeutic "class-based" effects when appropriate (e.g. as a recommended action, avoid the entire pharmacologic class).
	Use the medication name as ordered as well as generic ingredient drug names when identifying the interaction	— There may be confusion when the interacting active ingredient is not clearly identified (e.g. Rifater is the brand name of a combination product of isoniazid, rifampin and pyrazinamide, where the interacting ingredient may be rifampin).
Seriousness	Use consistent terms and definitions for DDI classification to indicate potential seriousness in a dialogue box	— Clearly conveying the reason for the alert and why it was assigned a given level of seriousness is useful for the clinician. — There may be confusion regarding the meaning and differentiation of terms such as 'critical' and 'significant.'
Clinical consequences (and frequency)	Clearly describe the potential clinical consequences of co-prescribing the interacting drugs in a dialogue box	— Alerts should describe the clinical consequences (e.g. hyperkalemia, QT prolongation, reduced efficacy leading to transplant rejection), rather than couch them in generic terms of a 'safety risk' or warning of unspecified dangers.
	When available, present the frequency or incidence of the clinical consequence associated with co-prescribing the interacting drugs	— When based also on the presence of other predisposing risk factors present in the patient this may be useful for estimating the risk of an adverse drug event for individual patients. — Estimated frequencies of DDIs are not usually known and likely to be underreported and therefore this field will remain largely unpopulated in the near term for many interactions. If this information is not known, this should be stated.