Module 6 – Individual Case Safety Reports (ICSR)

Contents

1. OVERVIEW OF ICSR PROCESSING

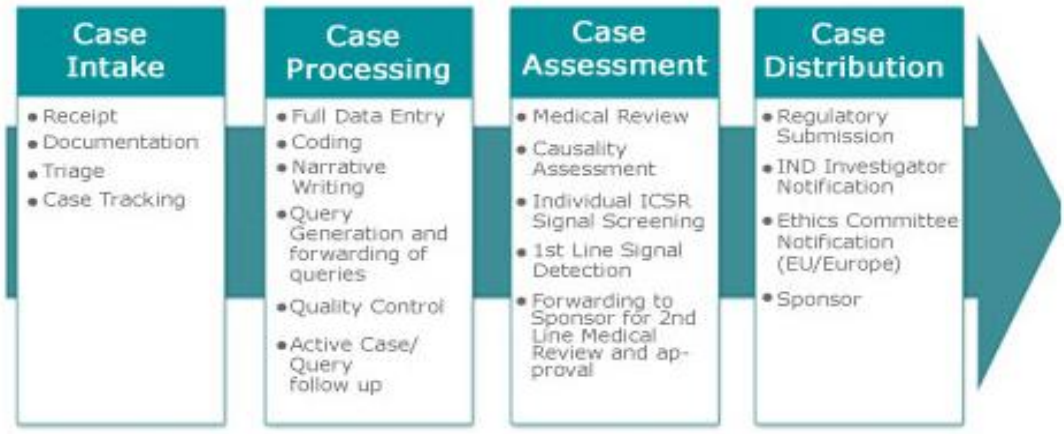
The case-handling process may be defined as the process by which single case reports (from clinical studies or from marketed use) are collected, evaluated and communicated.

A Serious Adverse Event (SAE) for a molecule could be generated during the preregistration or post-marketing phase. They could occur during clinical trials or be reported spontaneously by a patient, caregiver, relation, doctor, nurse or pharmacist. Another regulatory body or a licensed company could also be the informant. It could be received on phone, mail, fax, journals, newspapers or the latest social media.

Unexpected adverse events (AE) could arise anytime in the life of a product. These could put the user to serious risk and could curtail the life of the product. As part of the risk management plan, safety data is gathered throughout the life of a product. Consequently, every company that markets even a handful of products across many countries gathers thousands of reports per year.

Case processing is not detection of Adverse Drug Reactions (ADRs). It is merely the processing of ADR reports that the company receives from various sources.

The process of individual case processing involves the following steps: Case Intake, Case Processing, Medical Assessment and Distribution/Submission

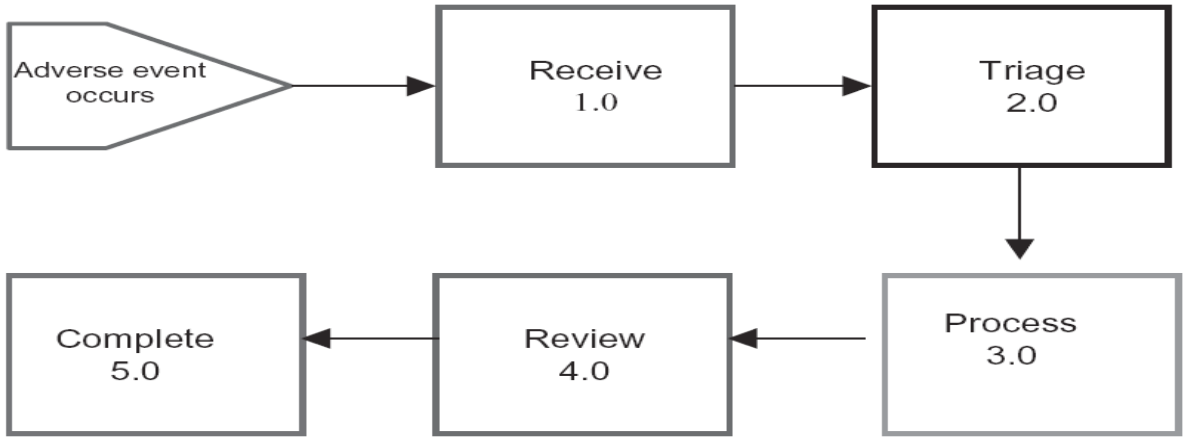


This process forms the basis for an important part of Pharmacovigilance (PV) and is a necessary prerequisite for enabling the company to comply with international regulations

for reporting to regulatory authorities. Although this may vary widely between companies, certain common tasks exist.

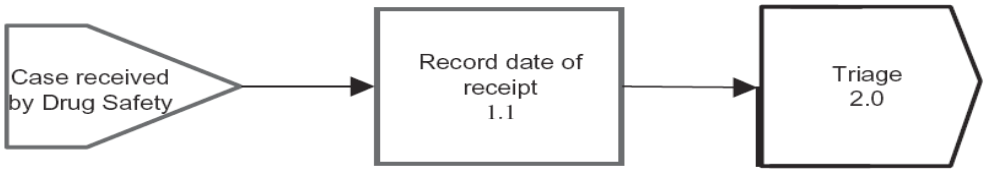
These tasks may be performed by different skill types, or they may be performed in slightly different sequences, but the steps described herein provide the basic framework of almost any case-handling process.

Simplified breakdown of activities is as given below:



2. CASE RECEIPT

Companies receive AE reports from a variety of sources via a wide range of methods. Each method of case receipt has special case-handling considerations, but the one absolute requirement for all is that the date of receipt by the company or company's agent must be captured and recorded, since this becomes the **clock start date** for regulatory reporting occurs.



- **Telephone calls:**

Consumers and healthcare professionals may call the company to complain specifically about side effects they believe to be caused by medications, or they may call the company for other reasons, for instance to obtain reimbursements or medical information, and incidentally mention an AE. The company employee or agent taking the call must be sufficiently trained not only to recognize AEs, but also to know what information should be collected concerning the event. Additionally, it is essential to obtain contact information enabling further follow-up with the reporter. If the calls are received in an area outside of the safety department, then a means must exist to transmit the information quickly.

- **Facsimile transmission:**

Although paper facsimiles, or 'faxes', have the advantage of providing automatic confirmation and date stamping, frequently there are legibility problems with the fax copies, and the use of faxes increases the amount of paper that must be tracked and archived. The use of 'e-fax' technology, in which faxes are automatically scanned into an electronic document that is received via electronic mail, allowing them to be viewed on-line and stored electronically, mitigates this problem.

- **Standard mail:**

Since letters containing AE information may conceivably be received by anyone in the company, it is essential that all personnel are trained in the recognition of adverse event related information and understand that this information needs to be forwarded to the safety department as soon as possible.

This training needs to include the highest levels of management within a company, since many times such letters are sent to the president or Chief Executive Officer (CEO) of a company. The legal department is also a frequent recipient of such correspondence, and every effort must be made to ensure that the safety department is notified promptly.

- **Electronic media:**

This category includes company electronic mail systems, company Web sites, Internet chat rooms, diskettes and compact discs, and electronic data capture systems used in clinical trials. The issues with electronic media are mainly issues of validity and verification.

Once the case is received from any source like Telephone, fax, email, licensing agreement, from the regulators or other companies, it is assigned to the triage team.

Prior to assigning the case to the triage team an acknowledgement of receipt needs to be sent to the reporter.

- **Acknowledgement:**

A valid case needs to have four elements; **an event, a reporter, a patient and a product (medicinal product/active pharmaceutical ingredient/vaccine etc.).**

Every report needs to be acknowledged, more so the valid reports.

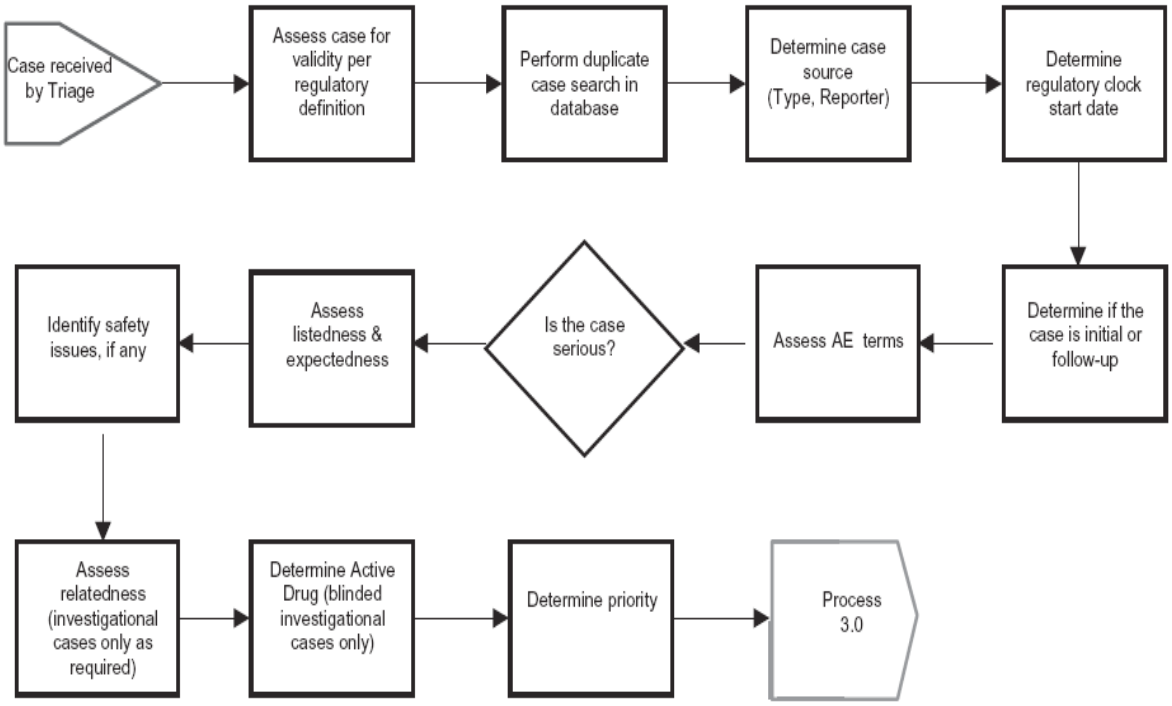
Acknowledgement establishes a contact with the reporter for more information whenever required. It builds company image with the stakeholder and also protects from litigation. A reporter may continue to send the same report repeatedly till it is acknowledged; hence this simple action avoids duplication.

3. CASE TRIAGE

Within the context of the case-handling process, triage is the assessment, classification and prioritization of the information received according to key regulatory, scientific and medical criteria.

Triage should be performed as early in the process as possible in order to ensure compliance with regulatory reporting timelines. Since this critical step in case handling has such a huge impact on the overall work of drug safety, experienced and qualified safety personnel should always supervise triage.

A detailed process map is presented below:



The essential components of Triage are presented below:

- **Case Validity:**

  A valid case needs to have four elements; **an event, a reporter, a patient and a drug.** Triage step checks the case for four valid criteria. Only valid cases are processed further.

Cases which do not have the above mentioned valid criteria are considered invalid and are archived after reasonable follow up for more information in line with company specific Standard operating procedures.

- **Duplicate search:**

  Due to, greater awareness, stringent regulations and multiple reporting sources, duplicate reports are a common phenomenon. Every safety database has a facility to identify and delete duplicates.

  Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, clinical trial code, country, etc.) may be used to identify duplicate reporting. This action is of significance for further processing of the case. The duplicate could actually be follow-up information that could alter the seriousness and hence reporting timeline of the case. Missed out duplicates could send misleading information.

- **Preliminary assessment of Seriousness, Expectedness and Reporting timelines**

  If the case is valid it is being evaluated for its seriousness and expectedness criteria.

A unique identity number is assigned to each individual case. The case is routed to the Data Entry Step in the workflow.

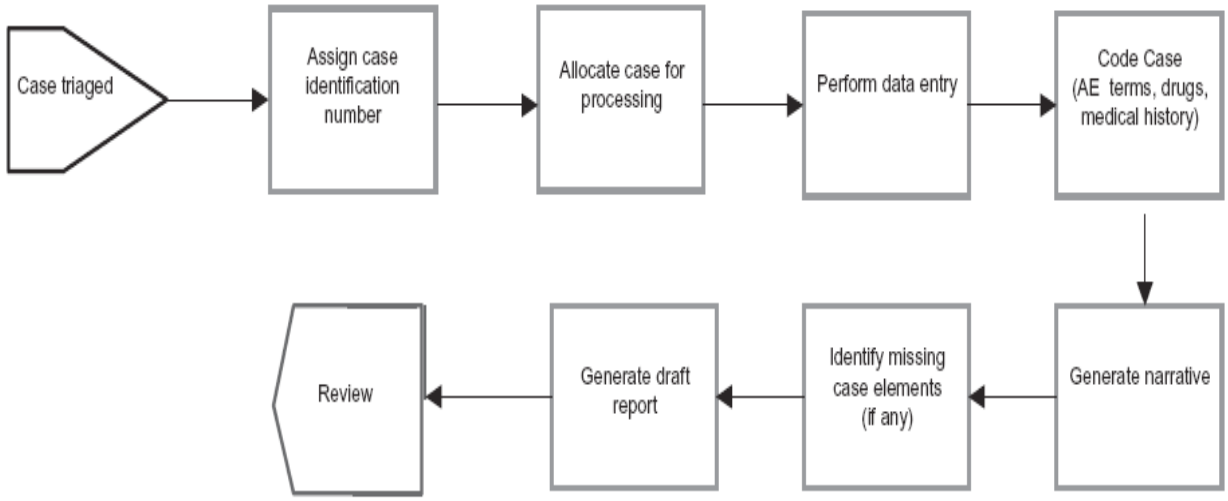
Triage in essentially a method of prioritizing the case for processing and reporting to authorities.

Case Triage is the most important step in the case-handling process, when one considers the impact on the rest of the workflow as well as the consequences of triage errors, e.g. late regulatory reports, missed safety signals and/or waste of case-handling resource. Key issues for consideration in the triage process include the need for clear communication of triage decisions to subsequent participants in the workflow of the case, adequate knowledge level of those involved in triage, and the need for appropriate checks and balances to ensure that errors are caught early.

4. DATA ENTRY

Data Entry includes the tasks of obtaining case specific information from the source documents and entering the applicable information in the safety database.

Furthermore, coding (AEs, medical history, concomitant conditions, concomitant medications, etc.), writing the case narrative and identifying missing information that should be pursued in follow-up are the other activities to be performed at this step



Data Entry:

The safety team member enters the case details into safety database; perform Medical Dictionary for Regulatory Activities (MedDRA) coding and drafting narratives of the case. In case of any query he/she asks for follow-up information to the reporter.

A seemingly repetitive and inconsequential step in the process; but this is something that forms the basis of good reporting. The quality of data entry affects the further processing of the case. Details of the four pillars of a valid case must be reported meticulously. Patient information must follow the HIPPA code for confidentiality. Reporter information must be clear and detailed enough to be able to contact the person if necessary.

Drug identifiers like name, formulation and dose have to be captured correctly.

Event report must be detailed enough for the evaluator to decide on the cause of the adverse event. This would include chronological description of the event or events, nature, localization, severity, characteristics of the event, results of investigations and tests, start date, course and outcome, concomitant medications and other risk factors.

Duplicate search: A repeat duplicate search is performed again at the Data Entry stage of the case to confirm the findings of Triage

Authoring the Case Safety narrative: The case narrative provides a summary to readers; who do not have access to original source data. During safety data management, it is seen and used by various groups like case reviewers to decide seriousness, upgrade etc., affiliate companies to triage for their countries, during preparation of PSURs and other summary reports and by regulatory authorities. **One should ensure completeness, chronology and sufficient detail in a narrative so that the reader is able to conclude.**

The case narrative contains the following essential elements:

- Patient demographic details
- Chronology or association in time (or place) between drug administration and event
- Medical or pharmacological plausibility based on signs and symptoms, laboratory tests, pathological findings, mechanism of action and treatment provided
- Current knowledge of nature and frequency of adverse reactions due to the suspect molecule; or the pharmacology
- Causality and Seriousness of the event

With the availability of the auto-narrative function in most safety databases, this step has particularly become more efficient however, the auto-narrative generated needs to be reviewed before finalization.

Coding of adverse reactions: This step ensures that everyone is talking the same language and the data can be shared internationally, most commonly used system is the MedDRA. Use of MedDRA has lead to a global standardization across regulatory

agencies, across companies & across countries. This step usually needs oversight by a medically qualified person.

Coding for drugs: Both the suspect drug and concomitant medication have to be coded. The principle is again to be talking the same language across countries, companies and regulatory bodies. Most common dictionary is the World Health Organization (WHO) Drug Dictionary enhanced. This is provided as a product by the Uppsala Monitoring centre of the WHO. Entries are updated four times a year. The majority of entries refer to prescription-only products, but some over-the-counter (OTC) preparations are included. The dictionary also covers biotech and blood products, diagnostic substances and contrast media. For chemical and therapeutic groupings, the WHO drug record number system and ATC classifications are considered.

Causality assessment: Non-spontaneous case reports usually indicate whether an adverse drug reaction is suspected due to the administered drug. In these circumstances and even otherwise, a causality assessment is required to be conducted. Various approaches have been developed for the structured determination of the likelihood of a causal relationship between drug exposure and adverse events. These systems are largely based on following considerations:

5. CASE REVIEW

After the data entry the case undergoes review.

Cases are reviewed after processing to ensure that regulatory, scientific and medical standards are met. Case review may be characterized as a two-step process:

- **Quality review:** The case is assigned to the QC team, where the QC person checks the work done by Safety associate.
- **Medical/scientific review:** The case moves in the workflow to the Medical Reviewer who assesses the case for Medical aspects, performs the causality assessment and gives a company comment on each case.

The key difference between the medical/scientific review and quality review concerns the focus of the review, rather than who does it, when it is done, or how it is done.

The appropriate focus of the quality review should be:

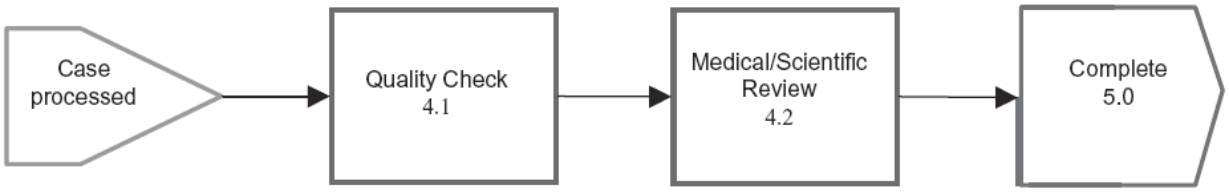
- **Confirmation of the triage assessment of regulatory reportability;**
- **Consistency of data-entry with source documents.**
- **Consistency with established report standards (ICH, 1995).**

In contrast, the appropriate focus of the medical/scientific review should be:

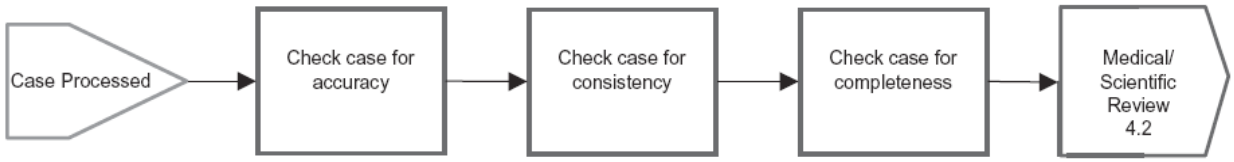
- **Appropriateness of the AE terms selected.**
- **Confirmation of the seriousness classification of the AE terms.**
- **Agreement with the listedness/expectedness classification of AE terms.**
- **Agreement with outcome classification.**
- **Agreement with the coding of AEs, concomitant conditions, and medical history.**
- **Review of the narrative to ensure that it makes clinical sense and includes all important elements**
- **Authoring the company clinical comment, including determination of the company causality assessment, when appropriate.**

- **Identification of any specific additional information needed for medical assessment purposes other than routine follow-up requests required for case completion. Pursuit of follow-up on single case reports should be tailored according to the importance of the case in terms of attempts made and methods used (CIOMS, 2001).**
- **Consideration of 'upgrade' or 'downgrade' to the case's regulatory reportability classification.**
- **Identification of potential safety signals.**

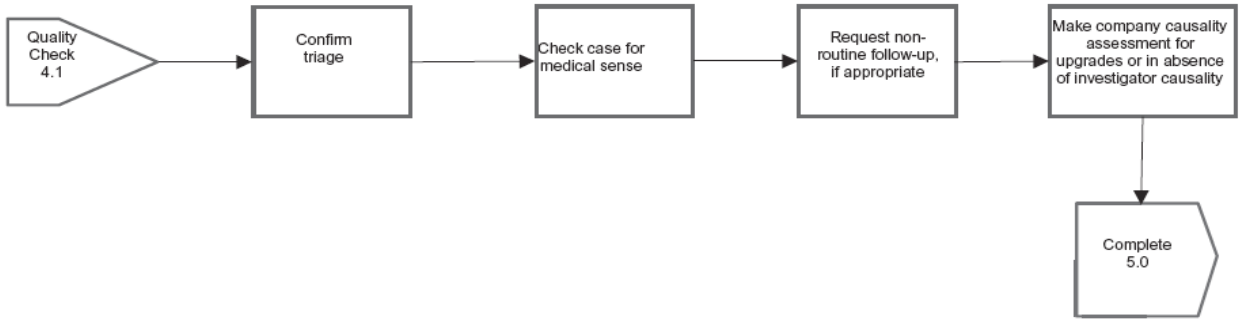
A rapid and clearly understood error resolution process must support case review.



Step 4: Case review



Step 4.1: Quality check



Step 4.2: Medical/scientific review

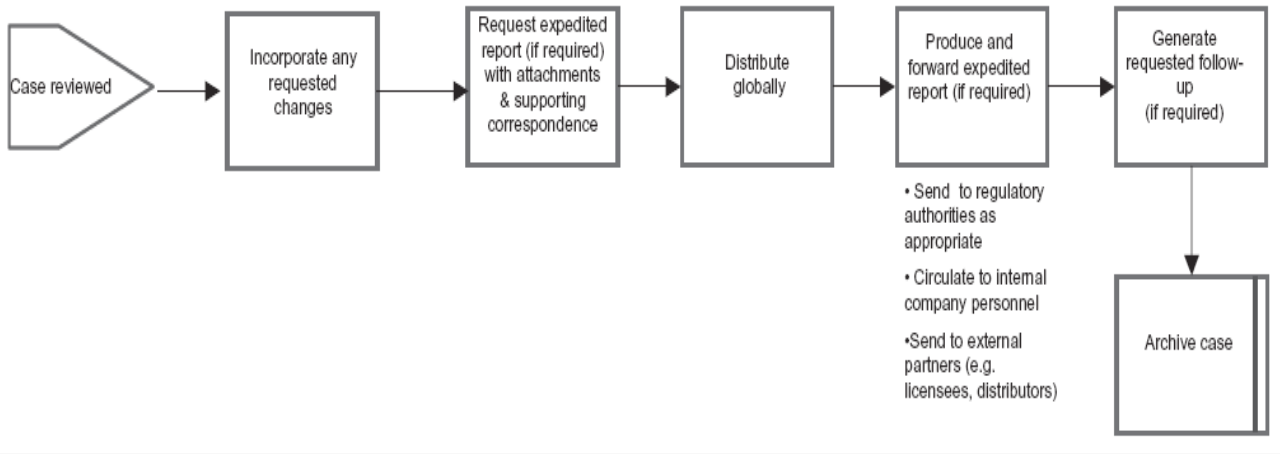
6. CASE COMPLETION

Upon completion of the Case Review step (Quality Review and Medical Review) the cases is deemed ready for submission to the regulatory authority. The submission team submits the case to the regulatory authority according to the global and local requirements.

The case completion process includes any updates to the case as required by the review cycle, incorporation of additional information requests into standard follow-up requests, generation of a final report and distribution of the final report to appropriate internal and external parties, which may include regulatory submission.

Completion also includes archiving the report and the accompanying source documents.

Strategies for document management should allow for paper as well as electronic storage.



Step 5: Case completion

7. SUMMARY OF CASE PROCESSING

An ICSR requires four essential parameters to ensure processing as a valid case – an identifiable patient, an identifiable reporter, at least one adverse reaction and at least one suspected company medicinal product.

Collection and appropriate handling and processing of ICSRs play an important role in Pharmacovigilance. The ICSRs reported for a drug in a given period are processed in a validated safety database. Per specified guidelines and timelines, expedited reports are reported to the appropriate Regulatory Agencies and Competent Authorities, and non-expedited reports are submitted as line listings in periodic reports. Carefully evaluated information obtained from these reports and the corrective and preventive actions taken on the drugs are used to develop the overall safety profile of the drug during pre- and post marketing phases.

The first step in Pharmacovigilance is the reporting of adverse events, either directly by the consumers or healthcare professionals/health authorities. Upon receipt of these reports, which are now called source documents, the case processing begins.

Processing of an ICSR includes the following steps:

1. Reviewing the source document for its completeness.

2. Creating the case in the designated validated Safety Database and entering all source document information.

3. Coding verbatim events using a pre-determined medical dictionary, usually the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and ensuring that the Lowest Level Term (LLT) is nearest possible match to the verbatim term.

4. Writing an accurate narrative in a chronological order of events, based on the information provided in the source document. The narrative includes all the information provided in the source document.

5. The data entered in the safety database is checked for completeness and consistency with the source document for the case by the Quality Check person.

Accurately processed cases ensure proper assessment of ICRSs, aggregate ICSR data, and the overall drugs' safety profile by a medical reviewer and when reported, ensure transfer of exact information (as received from the reporter) to the health authorities.

To ensure this, an efficient and effective approach to case processing should be sought and established as a primary objective.

The Safety department of an organization ensures that the above are followed through the effective deployment of standard operating procedures that govern the process and typically include the following:

1. Detailed training on the guidelines and regulations pertaining to the assessment of cases and the timelines for reporting etc.
2. In-depth training on the validated safety database (e.g. ARGUS, ARISg) that is used for case processing.
3. Development of appropriate data entry conventions and extensive training on the data entry conventions that will be used to process cases. This can be in-house or client-based conventions.
4. Development of coding procedures and guidelines and specific coding dictionary training (e.g. MedDRA, WHO Drug Dictionary).
5. Effective training on narrative writing.
6. Comprehensive training on the approved case processing workflow, which includes detailed training on each step of the workflow per specified roles and responsibilities and safety database access level.
7. Adequate product knowledge and constant up gradation on new safety information/signal(s) as they occur.

8. CONSIDERATIONS IN CASE PROCESSING

Following are the areas that need special mention in the context of processing ICSR's.

8.1 Seriousness

The generally accepted definition of seriousness is as follows:

A serious adverse event (experience) or serious adverse reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening ((NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition.

These should also usually be considered serious.

"Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse" (ICH E2A).

The European Union also notes that any suspected transmission via a medicinal product of an infectious agent is also considered serious.

Note that the FDA slightly altered the definition of "serious" effective March 2011 for clinical trials by adding the concept of "disability" directly into the definition, including the phrase: "substantial disruption of the ability to conduct normal life functions".

Over the years, these definitions have been discussed, parsed, and clarified by health agencies, companies, and other interested observers. In general, the most conservative interpretation is the one drug safety groups should use.

8.2 Expectedness

The United States regulations governing expectedness are fairly straightforward:

For a pre-marketed product: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator's brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents (21CFR312.32(a)). FDA added to this definition effective March 2011 by noting in 21CFR312 that "Unexpected, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation." That is, an AE in the class labeling section of the brochure without specific mention for the study drug is considered unexpected.

For marketed products: Any adverse drug experience that is not listed in the current labeling (package insert or summary of product characteristics) for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. AEs that are

"class-related" (i.e. allegedly seen with all products in this class of drugs) which are mentioned in the labeling (package insert or summary of product characteristics) or investigator brochure but which are not specifically described as occurring with this product are considered unexpected" (21CFR314.80(a)).

In the **European Union**, expectedness is addressed in Directive 2001/20/EC, which simply notes that an unexpected reaction is one "the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product)."

In theory, this concept is rather straightforward, but in practice, it becomes somewhat harder when synonyms and overlapping concepts are considered. In the report cited previously by Castle and Phillips, 72% of the European Union responders believed that if the labeled event is "dizziness," then "vertigo" would also be considered expected (labeled), but only 50% of the United States responders believed vertigo was labeled. Similarly, 18% of the European Union responders and 3% of the United States responders believed that if "hypotension, wheezing, and urticaria" are labeled, then a reported term of anaphylaxis would also be expected. Whether these differences persist, many years after the survey, is unclear.

However, it does highlight the fact that well-trained experienced medical personnel doing Pharmacovigilance can take the same set of facts and come up with differing and even opposing views.

In general, one should decide expectedness without thought to seriousness.

That is, just because a case is non-serious and the AE in question is mildly severe and of little medical import (e.g., a maculopapular rash) compared with a serious AE (e.g., severe hepatitis), the decision on expectedness should be made purely on the basis of the wording in the label and not on the seriousness. Give each AE its due.

With clinical trial drugs, especially those not yet marketed, there may be minimal or no human experience (e.g., the first study in humans or the first phase II study after phase I studies that showed no AEs). In this case, there are no labeled events in the investigator brochure, and everything is thus "new" and unexpected. Anticipated events based on the

pharmacologic properties of the drug should not be considered expected until actually reported in a patient and put into the brochure.

In some cases, it is necessary to consider the route of administration's, dosage's, or indication's being studied when assessing the expectedness. This usually depends on how the investigator brochure or marketed labeling is written. Some describe a different set of AEs for different indications, dosages, or routes of administration. Care must be taken to apply the correct label to each case when doing expectedness.

The general advice would be, as with seriousness, to decide on the side of conservatism. Then, if there are questions on whether an AE is expected, consider it unexpected.

8.3 Causality

Of the three criteria revolving around the regulatory reportability of an individual case (seriousness, expectedness, and relatedness), this one is often the most difficult to do for the multiple reasons explained next.

Causality may be determined initially at the individual case level, after the receipt of an individual case safety report and again after the review of aggregate data in a case series as for signaling, risk management, and various regulatory reports, such as PSURs.

First, some basic "housekeeping" points should be cleared up to ensure that cases are always handled and collected in the same manner. In doing case assessment, one should be sure that cases are coded using the same MedDRA version and codes (some older dictionaries may still be used and some labeling for older drugs may not be in MedDRA), with trained coders who use consistent methodology and synonym lists. For aggregate reports, the search criteria for the case series should be complete and standardized (using searches from the MSSO and/or CIOMS). Where possible, Standardized MedDRA Queries (SMQs) should be used.

Cases should be followed up (rapidly upon receipt, not at a later date) as appropriate to ensure the maximum amount of high-quality data.

In practice, many companies have two sets of standards and classifications for causality assessment of individual case safety reports. The first is used in clinical trials by the medical research group and the investigator (a separate causality assessment for each case should be done by the investigator and the sponsor as noted by FDA in the updating of the clinical trial regulations effective March 2011). The second is used in the drug safety unit. As there is no standard system, various categories (usually three to six) are used in case reports in clinical trials as follows:

- Related
- Probably related
- Possibly related
- Weakly related
- Unrelated
- Not assessable

This methodology is useful in later analyzing signals and in creating tables for investigator brochures, product labeling, and monographs to give a feel for the certainty or lack thereof about the causality of AEs by the drug in question. However, for the drug safety group, which has to determine whether a clinical trial case meets the three criteria (seriousness, expectedness, causality) for expedited reporting, the decision is **yes or no**. That is, the drug safety group must make the choice between unrelated and related. There is no middle ground or gray zone for causality here. Thus, the drug safety group has to make a rapid decision on whether the case is clearly unrelated (absolutely, positively) or everything else (possibly, probably, unlikely, weakly, etc.). Some drug safety groups consider "unlikely related" to be unrelated and other groups consider it in the broad "related" category.

Whichever way is decided, it should be made clear in writing in the SOP or working document (or the protocol for clinical trials) to everyone in the company what is done. Many drug safety officers believe that unless a case is clearly and absolutely unrelated, the causality should be, for reporting purposes, "related." To put it another way, the default causality for all cases is "possibly related" until there is evidence that the case is "unrelated." It is realized that this may not ultimately agree with the case analysis in the final clinical research study report, where a more nuanced opinion may be recorded. So, to

summarize, in drug safety there are two causality choices for reporting purposes: unrelated (thus making the case not reportable as an expedited case) and everything else. Effective March 2011, the FDA changed the causality regulations, introducing the concept of "reasonable possibility" (21CFR32): Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. This wording changes the older concept of "possible association" to "reasonable possibility." It is not clear that this will make a major difference in practice.

8.4 Expedited Reporting

Certain serious adverse events (SAEs) must be reported to health authorities within stipulated times. Most countries use "calendar days" rather than "business or working days," as holidays and working days are not the same everywhere. Some countries still retain different rules for local cases, but by and large, thanks to ICH, CIOMS, and common sense, most countries have standardized on the same timing, format, and content of expedited (also called "alert") reports.

Clinical Trial Reporting

Another way to express "clinical trial reporting" is reporting for drugs that are not yet marketed (no Marketing Authorization or New Drug Approval (NDA) yet or for the indication in question). Although this refers primarily to clinical trials, it may also refer to SAEs found in named patient use, compassionate use, solicited SAEs, epidemiologic trials, and other "nonclassic" trials and studies. Most countries require that SAEs, which are unexpected (not labeled), that is, do not appear in the product labeling that is usually the Investigator Brochure, and that have some possibility (even if small) of being caused by the study drug in question, be reported in 15 calendar days from the first notification of anyone in the company (or organization), including its agents, business partners, contractors, distributors,

and vendors. This is called a “15-day report,” “an expedited report,” or “an alert report.” Note the triple requirement: serious, unlabeled, and possibly related. A subcategory of this is the “7-day report.” In a 7-day report, the patient in question has died or had a life threatening SAE, which is also unexpected and possibly related (same as above). This report must be sent to the health authorities within 7 calendar days. Note that all 7-day reports are also 15-day reports. Thus, if a report is communicated as a 7-day report, it must also be followed up as a 15-day report. The 7-day report may be communicated as a phone call, fax, or some other less formal communication compared with the more formal 15-day report (a CIOMS I, Med Watch form, E2B transmission).

If the 7-day report is “informal,” then it must be followed up with the usual 15-day “formal” report. If the 7-day report is the CIOMS I, MedWatch form, or E2B, it will cover both requirements. Thus, the 7-day report becomes a 15-day report with the same requirements for follow-up and further reporting (see below).

United States Requirements for Expedited IND Reports

The Investigator’s New Drug Application (IND) obligations are found in 21CFR312. An IND is usually opened and held by a pharmaceutical company, but academics, universities, and individuals may also do so. The term that the FDA uses for the IND holder is generally “the sponsor.” The sponsor is obliged to “review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator” (21CFR312.56(c)). This includes 7- and 15-day expedited reports (21CFR312.32) and annual reports (21CFR312.33). In March 2011, updates to these regulations went into effect.

Expedited IND Reports (Alert Reports, 7- and 15-Day IND Reports)

Serious, unexpected (unlabeled), adverse events from clinical trials for which there is a reasonable possibility that the drug caused the event must be reported. Each report identifies all similar reports sent to the FDA, and the sponsor analyzes their significance.

Specifically the FDA regulations state 21CFR312(c) (1): “The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator’s IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15

calendar days after the sponsor determines that the information qualifies for reporting." In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction considering previous, similar reports or any other relevant information. In each expedited report, all previously submitted expedited reports of similar suspected adverse reactions must be noted and analyzed considering previous, similar reports or any other relevant information. This analysis may be included in the narrative.

European Regulatory Requirements

In the EU post-marketing environment, an Individual Case Safety Report (ICSR) may involve a serious or non-serious adverse reaction – regardless of expectedness.

EU pharmacovigilance laws require that ALL spontaneous serious adverse reaction reports must be expedited within 15 days. In addition, from 22nd November 2017 all non-serious adverse reactions, with an origin within the EU, will require expediting to EMA within 90 days.