Module 6: Individual Case Safety Reports (ICSR)

Introduction

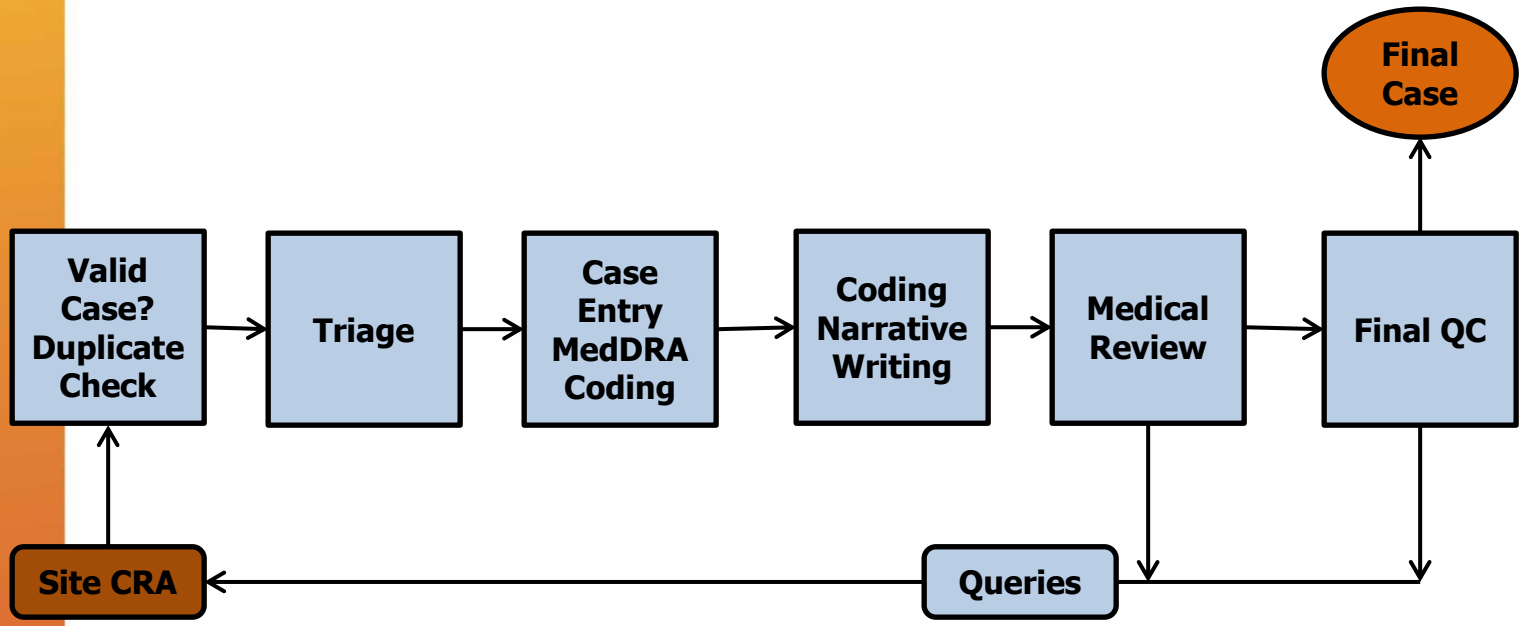
- ICSR is defined as an individual case safety report where information is provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time

- Safety information is processed in safety databases (e.g., Argus, Arisg, AERS (AWARE)) for regulatory purposes and signal detection

- Data generated from ICSR's helps monitor patient safety

- **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.

SAFETY CASE PROCESSING AND REVIEW



CRA: Clinical Research Associate
MedDRA: Medical Dictionary for Regulatory Activities

ICSRs: What constitutes a valid report?

ICSRs: Individual Case Safety Reports

- An identifiable patient
- An identifiable reporter
- At least one suspect drug
- At least one suspected reaction

Information Collected in ICSRs

- Patient
- Reporter
- Event
- Drug
- Medical history including concomitant medications and conditions
- Laboratory Data
- Narratives/texts
- Special situations: Lack of effect, overdose, drug abuse, drug dependence, medication error, technical complaints; pregnancy cases

Types of ICSRs – Clinical Trials (1)

Solicited

(Interventional/ Non-Interventional) Reports

Clinical trials

Registries, post-authorisation named-patients use programmes

Post-authorization safety studies (PASS)

Other patient support and disease management programmes

Surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

A patient support programme is an organised data collection system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products.

For the purpose of safety reporting, solicited reports **should not be considered spontaneous but** classified as ICSRs from studies and therefore **should have an appropriate causality assessment by a healthcare professional or the MAH** (see Annex IV, ICH-E2D).

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

Types of ICSRs –Non-interventional trial/study

- A study where the medicinal product(s) is (are) prescribed in the **usual manner** in accordance with the terms of the marketing authorisation.
- The assignment of the patient to a drugis not decided in advance by a **trial protocol** but as per current practice
- No additional diagnostic or monitoring procedures shall be applied to the patients

Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data).

Non-interventional studies also include those involving primary data collection (e.g. prospective **observational studies and registries** in which the data collected derive from routine clinical care), provided that the above mentioned 3 conditions are met.

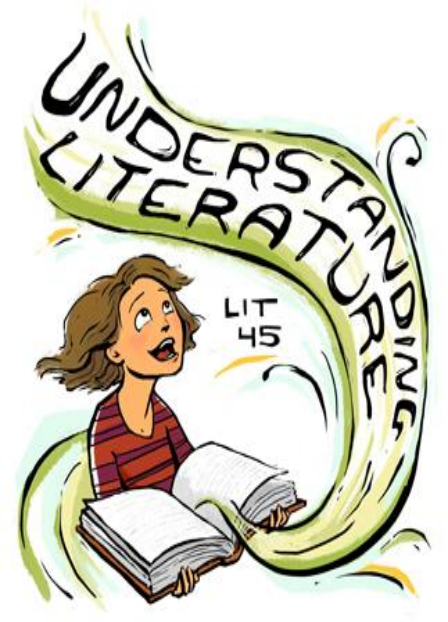
Types of ICSRs (3)

Unsolicited Reports

- An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that **does not derive from a study or any organised data collection scheme** (see Annex IV, ICH-E2D).
- **Spontaneous Reports**
- **Stimulated Reports**
- Literature reports
- Other sources: e.g. law suit (**Legal**) cases, **media** cases: e.g. lay press /internet/digital media.

Consequently AEs arising from the use of social media to gather market research information i.e. digital listening will be unsolicited reports **whilst** those cited during any other form of online market research, face to face, telephone or postal market research will be solicited reports.

Types of ICSRs – Literature Reports (4)



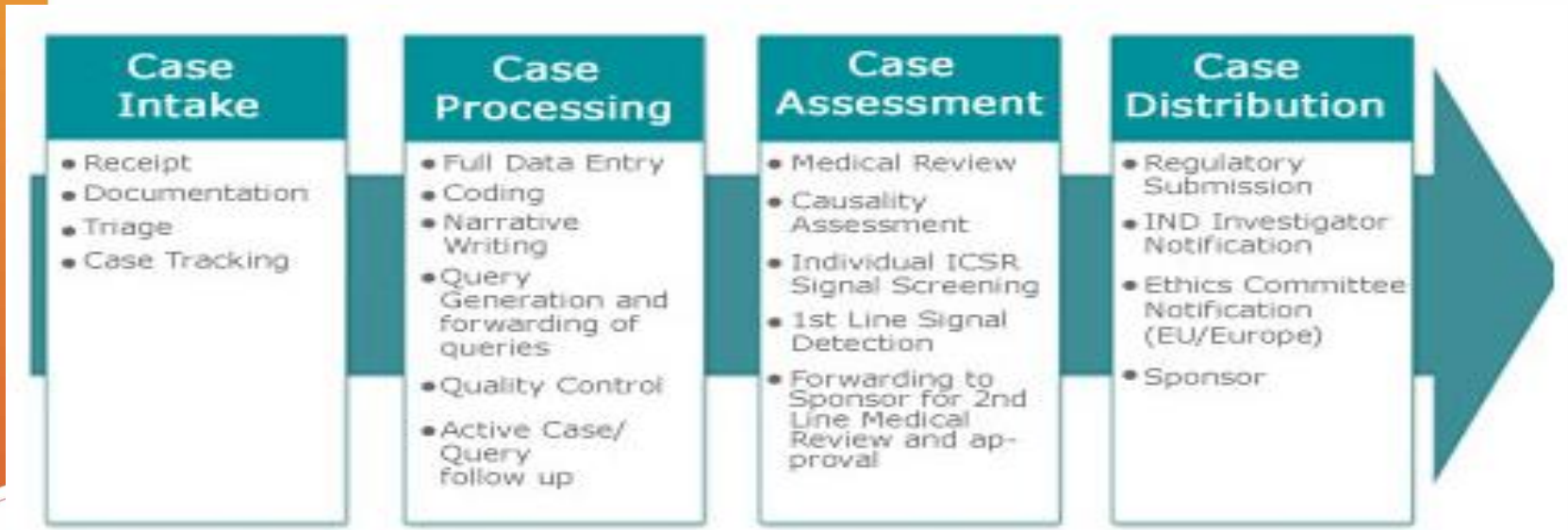
MAH (Marketing Authorisation Holders) are expected to maintain awareness of possible publications through **a systematic literature review** of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) **no less frequently than once a week.**

Global literature databases such as Pubmed (MedLine) or Embase (or any other client specific databases) are searched to identify **VALID** articles and abstracts to:

- Be processed as ICSRs
- Be included in PSURs/PBRERs
- NDA AR (New Drug Application Annual Report)
- DSUR (Development Safety Update Report)

Overview of ICSR Processing

Case receipt → Triage → Case analysis → Peer review → Medical review → Quality review → ICSR completion



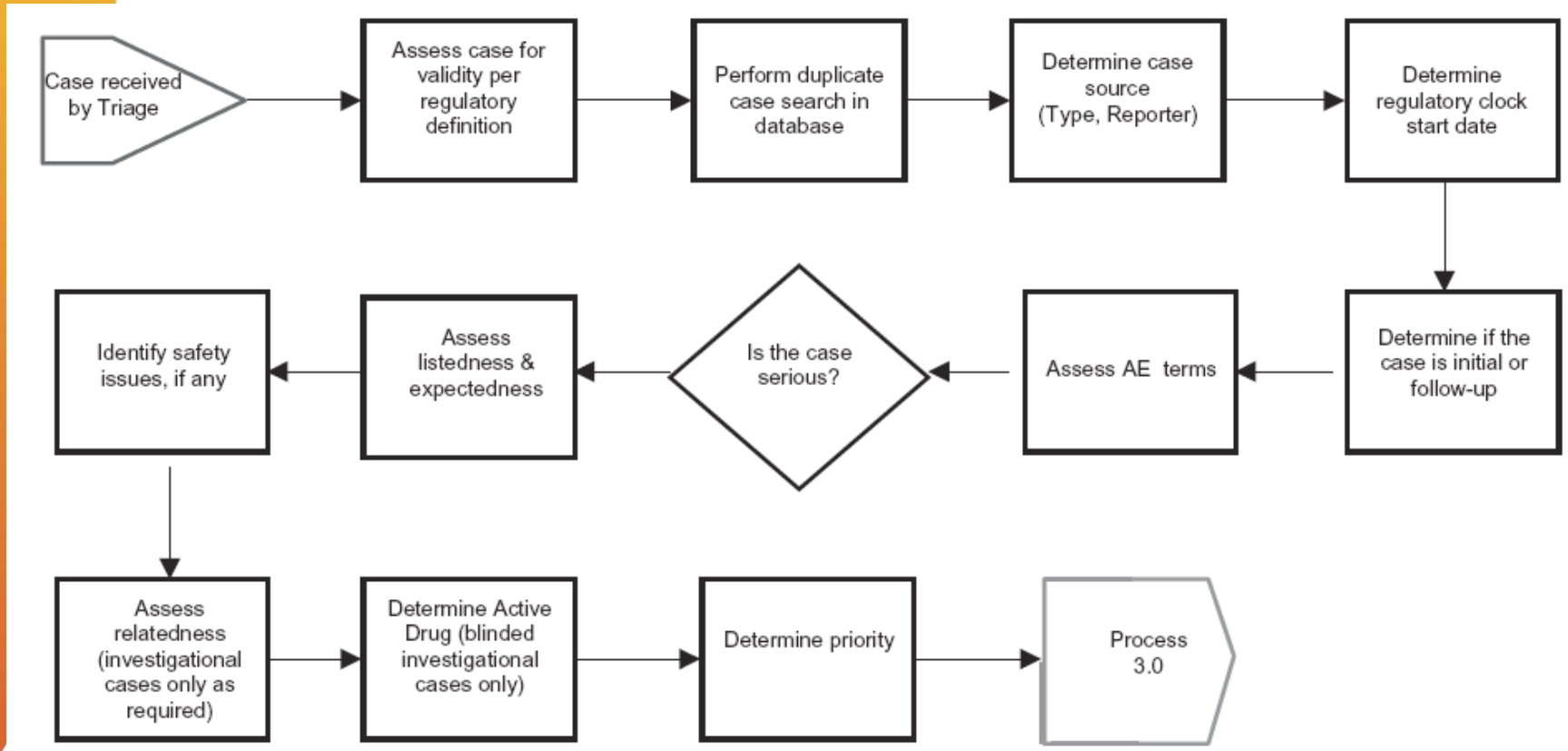
Case Receipt

- Companies receive AE reports from a variety of sources via a wide range of methods:
  - Telephone calls
  - Facsimile transmission
  - Standard mail
  - Electronic media
- Once the case is received from any source, 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.
- 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 purposes.

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 and includes:
  - **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.
  - **Duplicate search:**
  - **Preliminary assessment of Seriousness, Expectedness and Reporting timelines**

Case Triage – Detailed Process Map



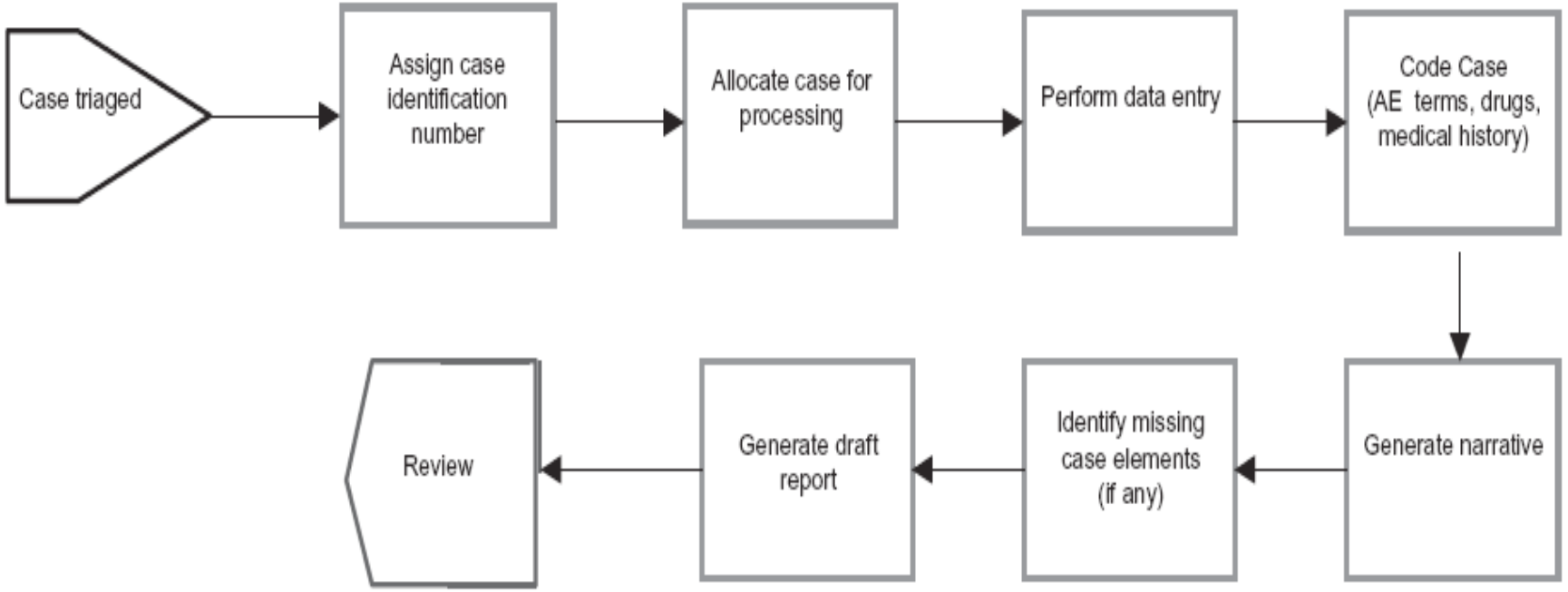
ICH Validity Criteria of ICSR

- According to ICH Guideline E2D, it is recommended that as much information as possible be collected at the time of the initial report. However, for the purpose of regulatory reporting, the minimum data elements for an ADR case are:
  - an **identifiable reporter**,
  - an **identifiable patient**,
  - an **adverse reaction**,
  - a **suspect product**.
- Lack of any of these four elements means that the case is considered incomplete; however, MAHs are expected to exercise due diligence to collect the missing data elements. For regulatory reporting, a case should meet the following minimum criteria.

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.
  - Report type of case, local reference number, country of incidence, reporter details and patient details.
  - patient medical history (including family history and past drug events) and relevant lab data (with or without units).
  - adverse event details
  - product details (suspects, concomitants and treatment drugs).
  - Coding medical history, AEs, product indications and lab data
  - Coding products using appropriate drug dictionaries.
  - Capture reporter's causality assessment.
  - Perform labeling/listedness/expectedness of adverse events.
  - Add administrative comments or communication if any
  - Verify if the case is an initial or a follow up report

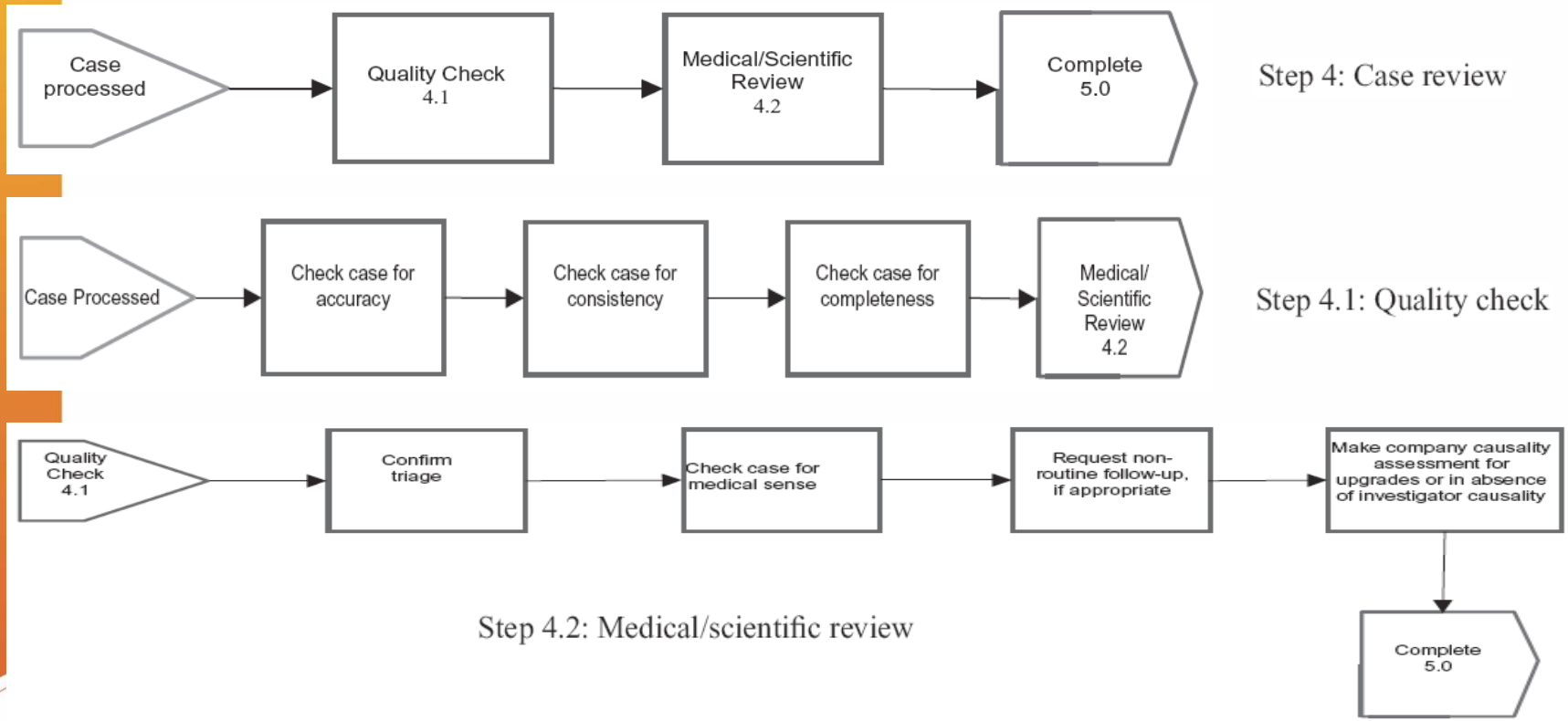
Data Entry – Detailed Process Map



Case 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.

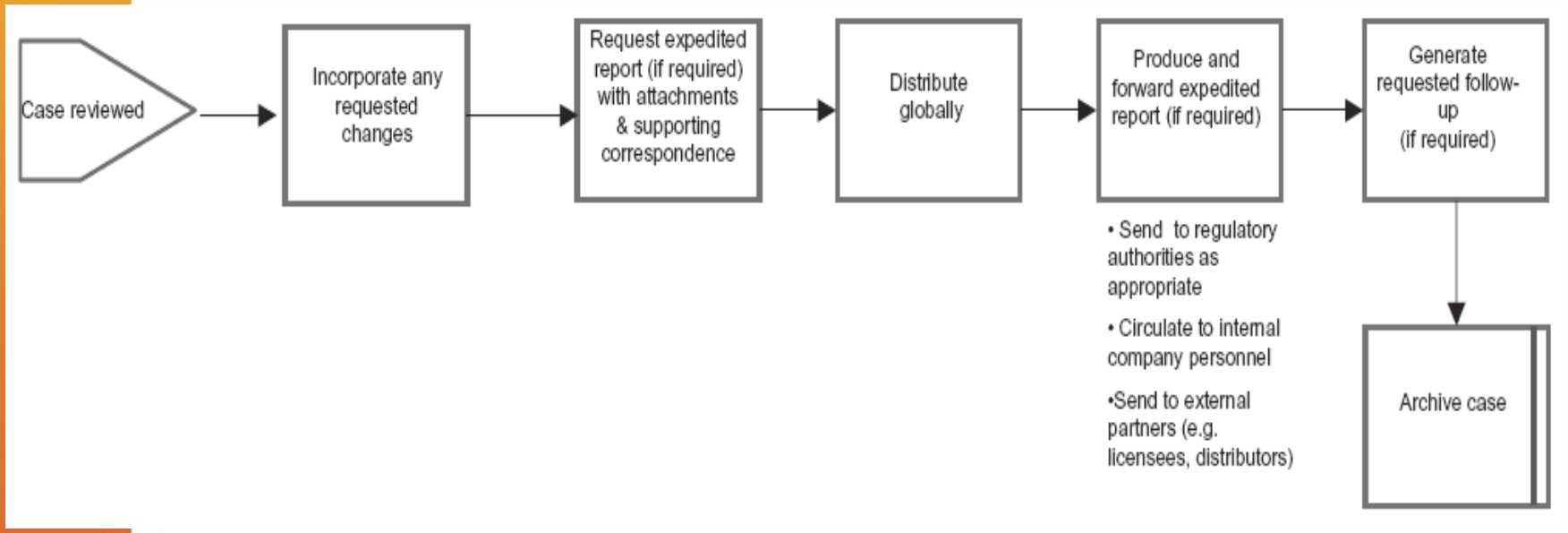
Data Review – Detailed Process Map



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 local requirement.
- The case completion process includes any updates to the case as required by the review cycle
- Completion also includes archiving the report and the accompanying source documents.
- Strategies for document management should allow for paper as well as electronic storage.

Case Completion – Detailed Process Map



Step 5: Case completion

Sources of ICSRs

- Solicited (derived from organized data collection systems)
  - Clinical trials, Registries
  - Post-approval named patient use programs
  - Other patient support & disease management programs
  - Surveys of patients or healthcare providers or information gathering on efficacy or patient compliance
- Unsolicited
  - Spontaneous
  - Literature
  - Internet
  - Regulatory authorities
  - Other sources: lay press or other media

Initial and Follow-up Cases

Cases can be categorized in two different subsets:

Initial cases:

- The minimum information required for the submission of an initial case report is an **identifiable patient**, an **identifiable reporter**, a **suspected reaction**, and a **suspect drug**. While the report recipient is encouraged to actively query the reporter to elicit the most complete account possible, inferences, and suggestions should be avoided in report submission

Follow-up cases:

- The relevant information, which was not available in the initial case, should be asked specifically for documentation in the follow up case

  In exceptional circumstances, if the reporter has refused requests for information, a regulatory authority might be able to assist in obtaining follow-up data

Seriousness

Adverse events are considered serious if meeting one or more of the below criteria :

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability / incapacity, ("persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.)
- Is a congenital anomaly / birth defect,
- IME (Important Medical Event) or medically significant events - 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 definition of seriousness - **ICH E2D**

Causality

- Causality is also known as relatedness or causal relationship
- Refers to determination of the '**suspect causal relation**'
- All **spontaneous & Literature** reports are deemed **related**
- In trials if either the **investigator** or the **sponsor** assesses the event as related the report becomes **related**
- For case handling purposes, spontaneous cases are initially deemed related; however, for signal detection and assessment purposes, the company has to give a causality statement.

Expectedness\Labeling\Listedness

- **Expected:** An AE from a clinical study is assessed as expected if it is described in the single reference safety document described in the protocol such as investigational brochure

- **Labeled:** An AE is assessed as labeled in the US Package Insert (USPI)/Summary of Product Characteristics (SPC)/local product document (LPD) if it is described, in terms of specificity or severity, as consistent with the safety sections contained in the current USPI/SPC/LPD

- **Listed:** An AE is assessed as listed if it is described, in terms of specificity or severity, as consistent with the safety sections contained in the Core Data Sheet (CDS)

- **Unexpected/Unlisted/Unlabeled:** An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the reference safety information labeling

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,”
- 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.
- One of the most common causes of critical findings in Drug Safety Inspections is the non-compliance with the expedited reporting of spontaneous adverse drug reactions

Questions?