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Handling and Processing Safety Reports from Clinical Trials and Spontaneous Origin

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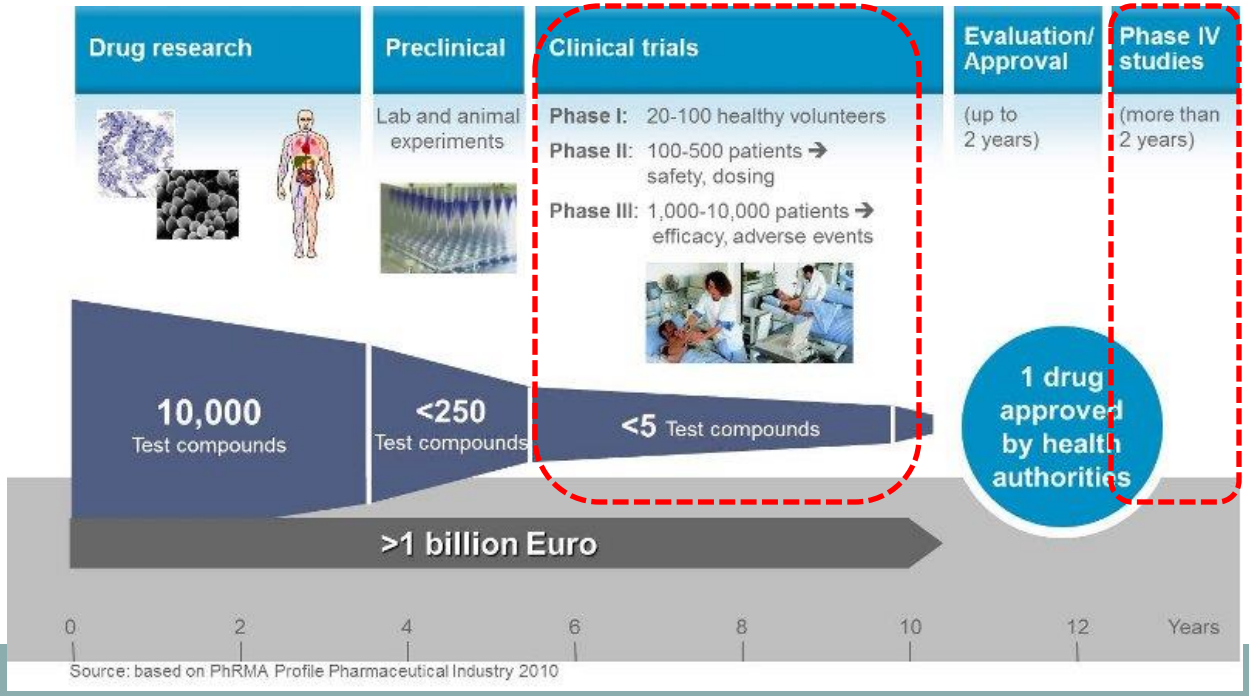
Faridkot, India.

- Individual case safety reports (**ICSRs**) and the Serious adverse event (**SAE**) reporting is most commonly associated with Pharmacovigilance (PV).

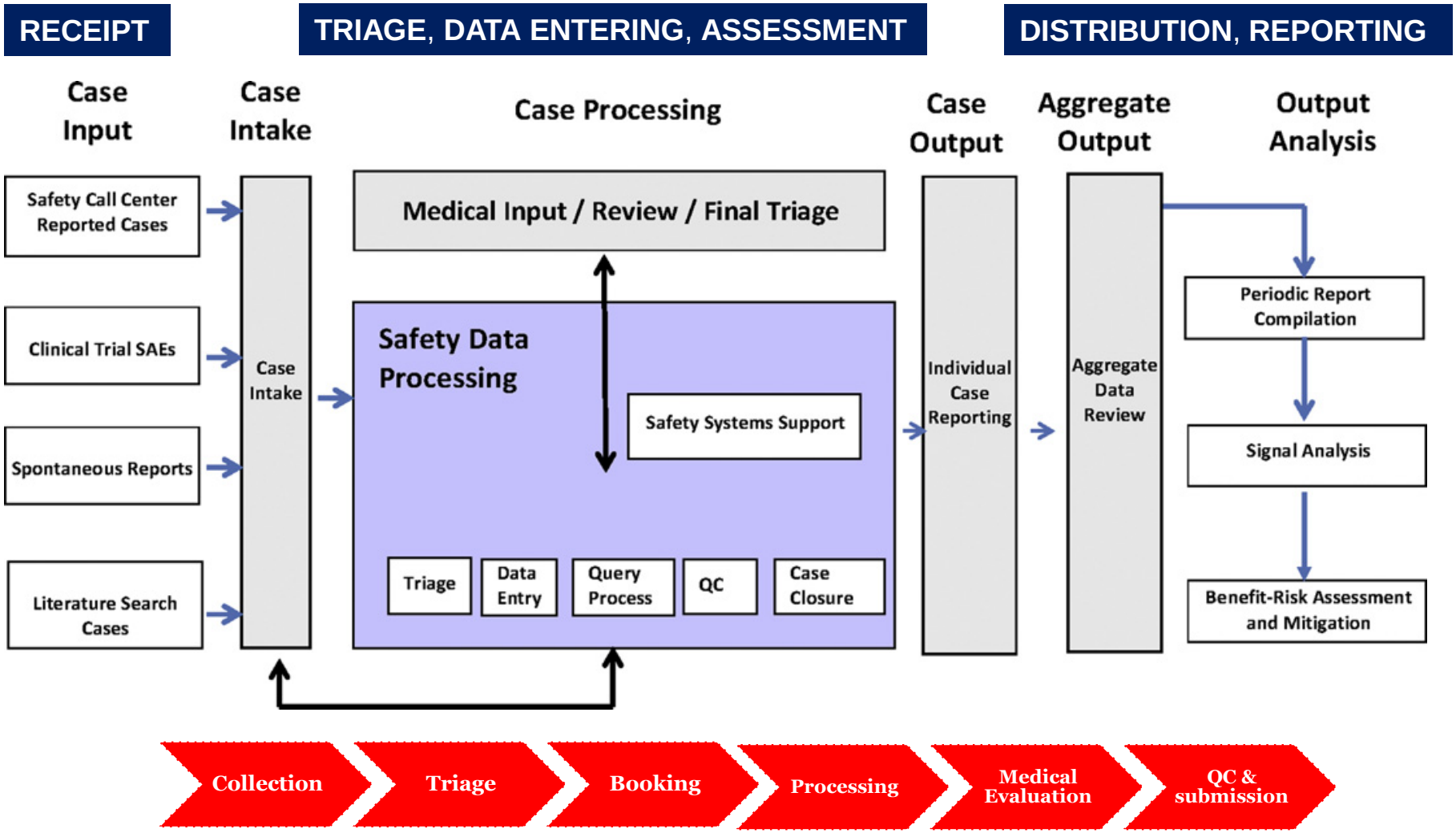
- Adverse event (AE) reporting consumes a **significant amount of resources** for drug regulatory authorities and drug safety departments in pharmaceutical companies.

- AE reporting starts as soon the new drug molecule is introduced to the humans during clinical trials.

- Adverse event (AE) reporting involves the **receipt**, **triage**, **data entering**, **assessment**, **distribution**, **reporting**, and **archiving of AE data and documentation.**



Collection, processing and submission of safety reports



Step 1: Case Input or AE collection

- It involves collection of adverse experience information from multiple sources.

- Traditional sources are **clinical trials** and **spontaneous reports**

- Other sources of information include:
  - Solicited reports from patient support programs
  - Surveys
  - Epidemiological studies
  - Post marketing studies (PMS)
  - Disease registries
  - Drug Regulatory Authorities and other database
  - Licensor
  - Media (including social media and websites)



Step 2: Case Triage or Case assessment

- Complaint is receive at the PV department and is classified for processing.

- **Activity 1:**
  Reports is **date stamped** when received (generally should be done within 24 hours of receipt).

- **Activity 2:**
  Initial triage is performed by DSAs to determine whether the report needs **urgent processing** (SUSARs, high priority reports).

- **Activity 3:**
  Triage also covers **validation of case report** **for accuracy, completeness and bonafied information** as per regulatory requirements i.e:
  - Identifiable **patient**
  - Identifiable **reporter**
  - Suspected **drug**
  - **Adverse drug reaction**/Product quality complaint.

The "4 Elements" of an AE case

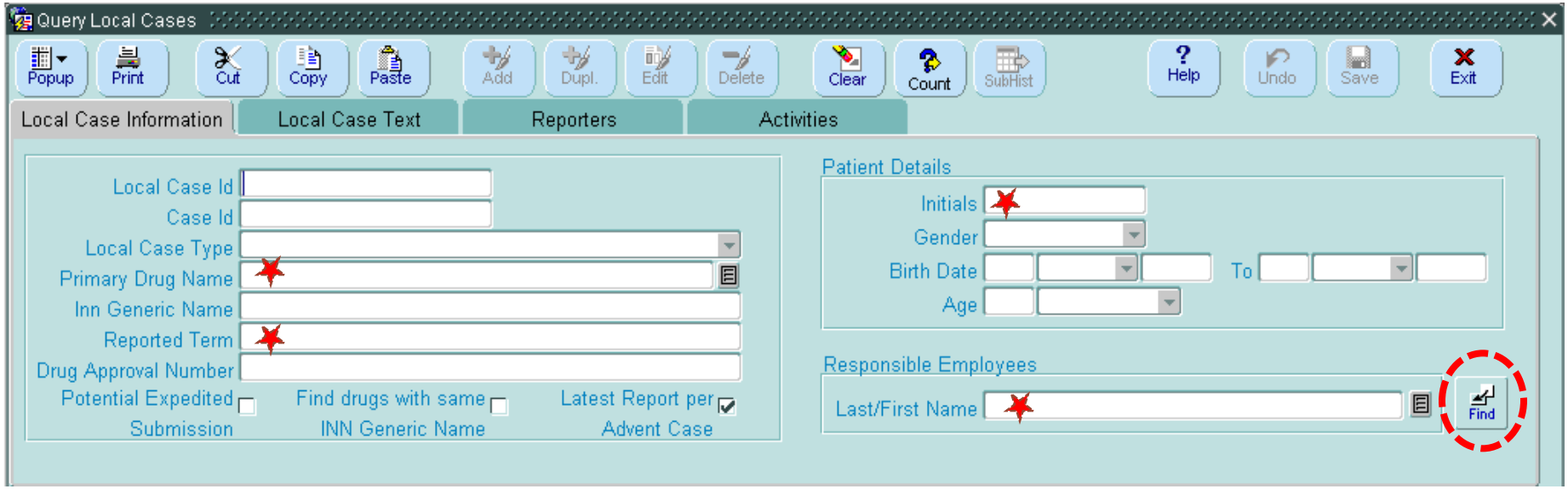


Step 3: Case booking and processing

- Following triage, the **case information is entered into a computerized safety database**.
- Drug safety database (Aris G, Argus, etc) is designed to collect safety data in an organized manner.
- Various **mandatory fields** are filled by the data entry personnel e.g. date of receipt of ADR, patient, reporter, AE, suspected drug, seriousness criteria and reporter causality assessment.
- Other required information as per local regulations include: type of source (spontaneous, literature, clinical trial) and **duplicate check**.
- Once minimum information is entered for reporting, the case is saved and assigned a **manufacturer control number** (MCN).



Step 3: Case booking (Spontaneous cases)

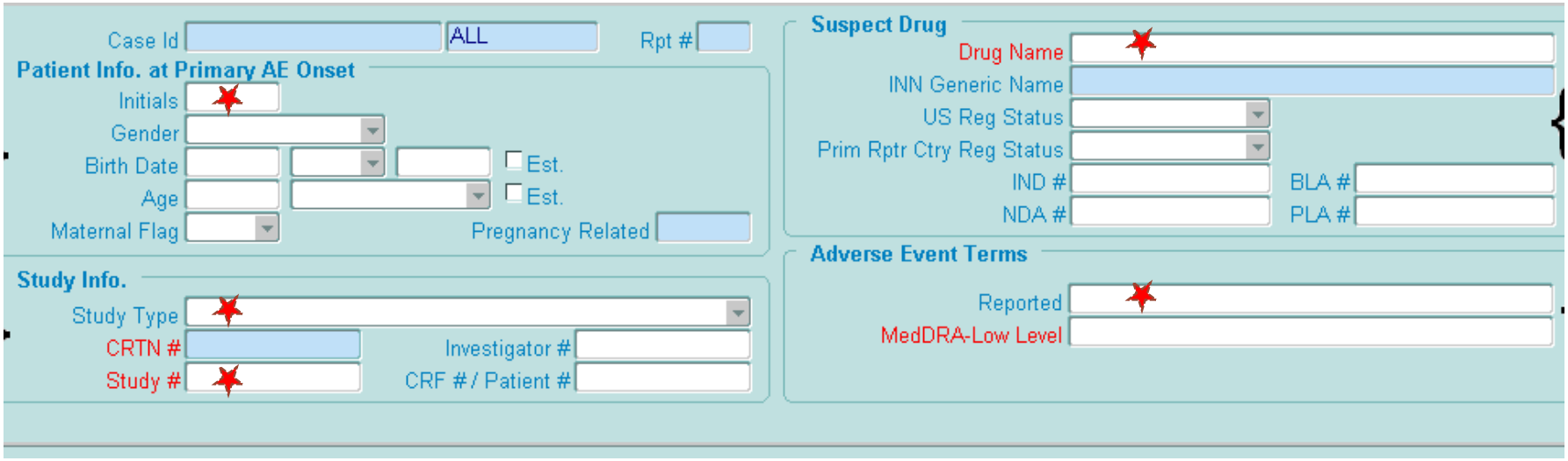


- **Drug**
- **AE**
- **Patient initials**
- **Reporter**

❑ Low stringent conditions are considered to accurately perform a duplicate check.

❑ If **no duplicate is found** then the case is booked and a unique **MCN is generated.**

Step 3: Case booking (Clinical Trial)

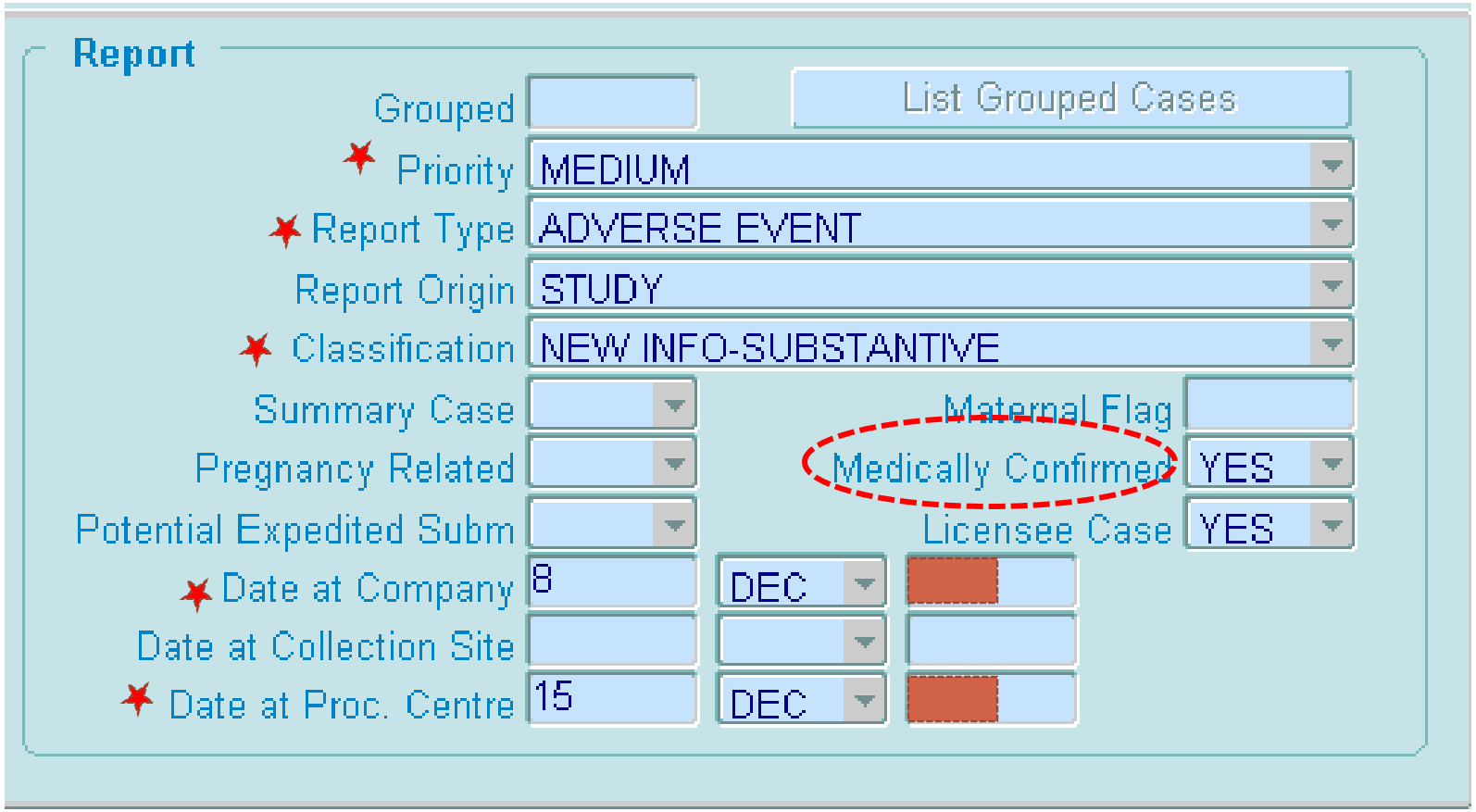


- **Drug**
- **AE**
- **Patient initials**
- **Reporter**
- **Study details (type and number)**

❑ Low stringent conditions are considered to accurately perform a duplicate check.

❑ If **no duplicate is found** then the case is booked and a unique **MCN is generated.**

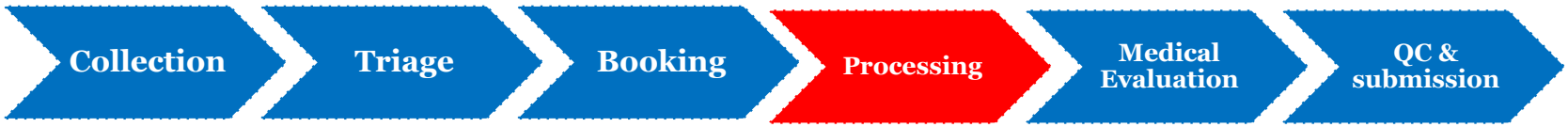
Additional information is added during case initiation



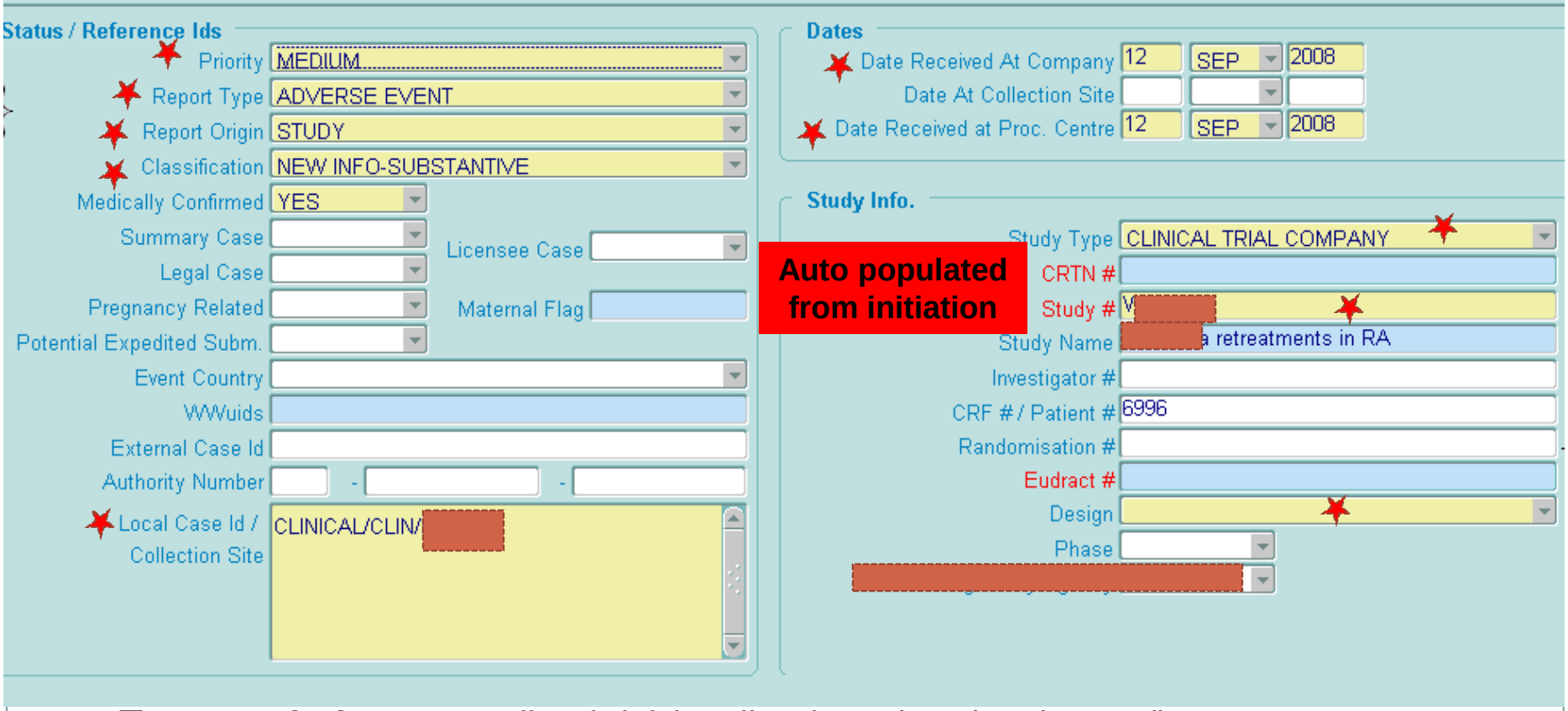
Case processing by DSA/ PV scientist

- DSA add all the information reported in **the ADR Reporting form** (CIOMS Form/ MedWatch Form)

- Other activities include entering the following information on drug safety data base:
  - **Narrative writing**
  - Findings of **laboratory investigation**
  - **Company causality assessment**
  - and **labeling** of ADR (USPI, CDS, IB, Local document)
  - **Query** for more information or if any discrepancy
  - **Data review**/validation

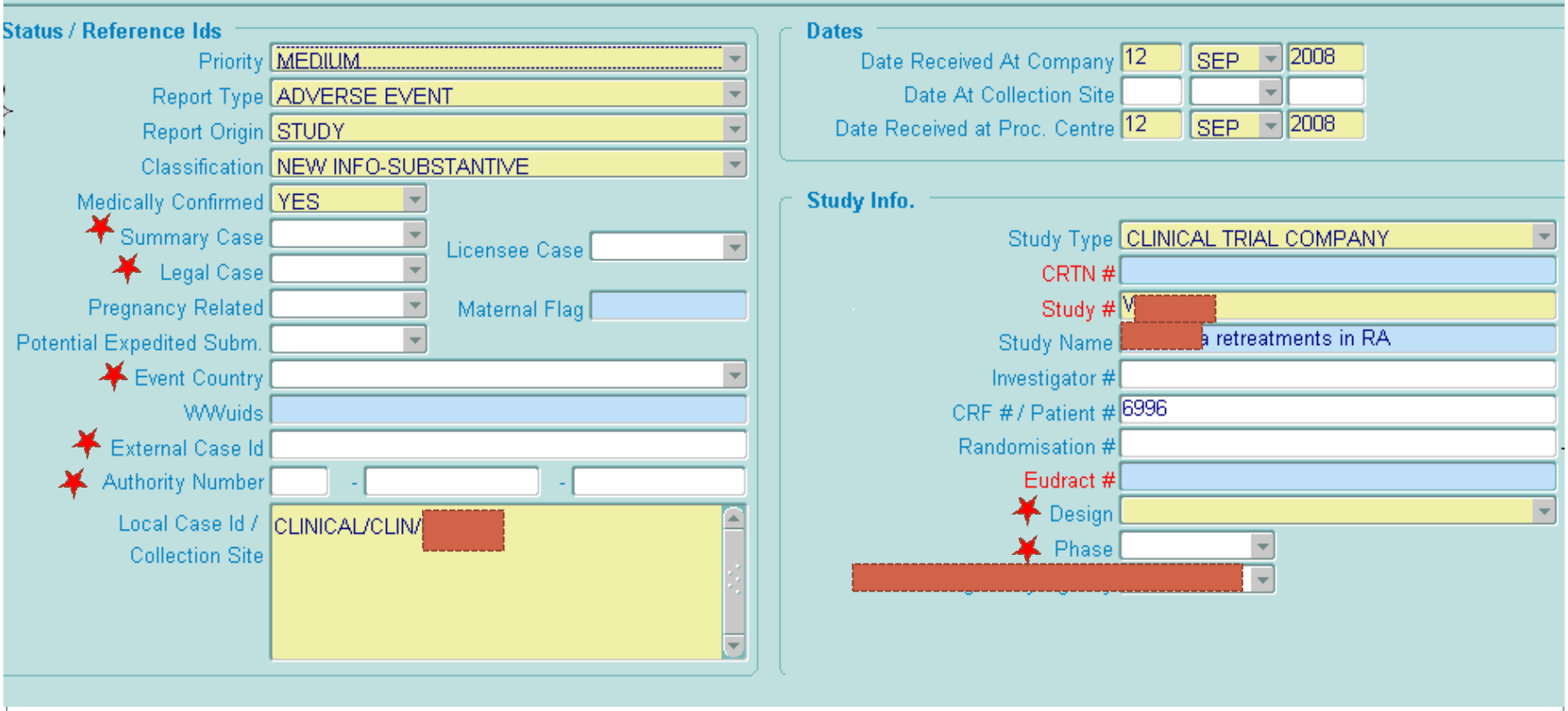


1) Report Screen



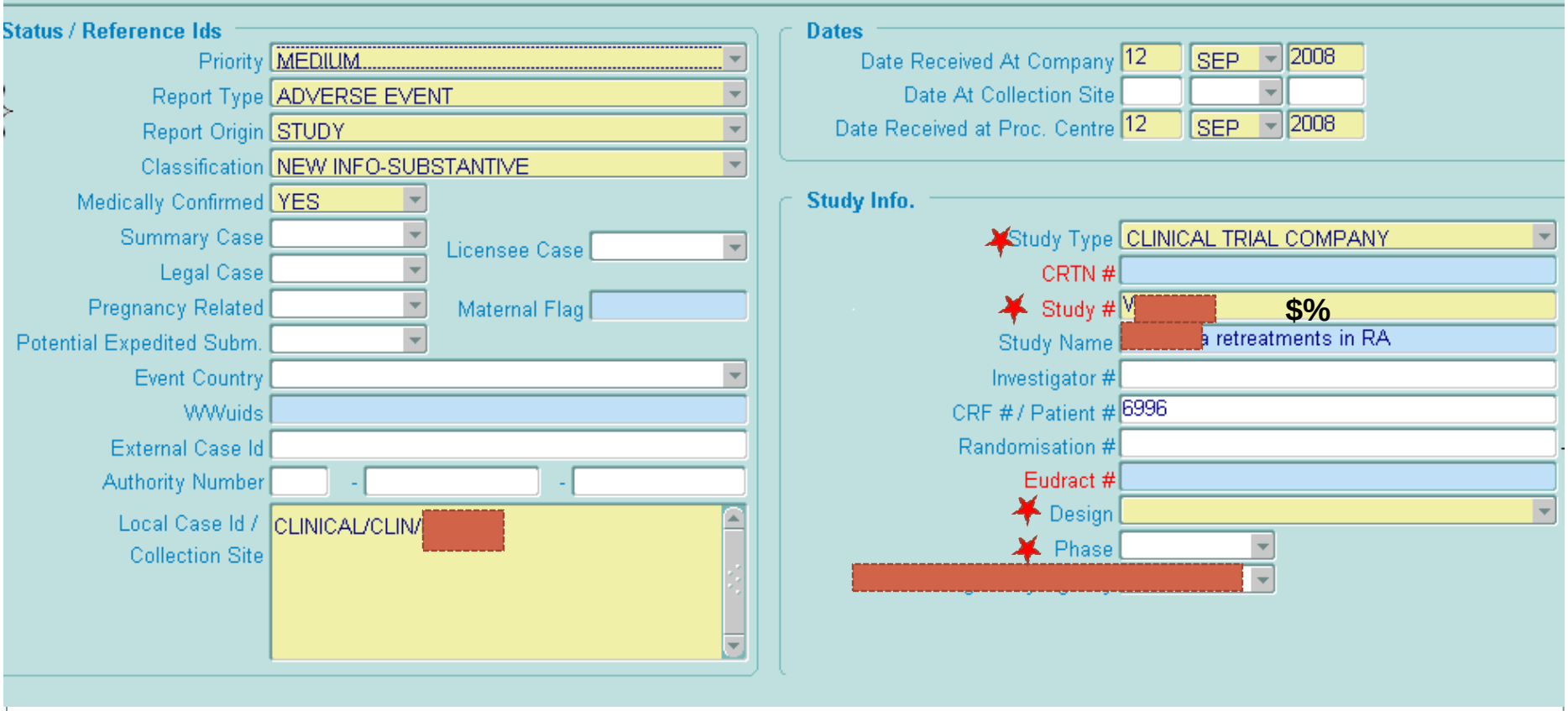
- **Case priority**: Immediate/High/Medium/Low (can be changed).
- **Report Origin:** Study/ spontaneous
- **Classification:** New info substantive/ non-substantive, data correction substantive/ non-substantive
- **Medically confirmed:** All study case or Health Authority (medically confirmed) , spontaneous case (depends on reporter)

1) Report Screen (Cont..)



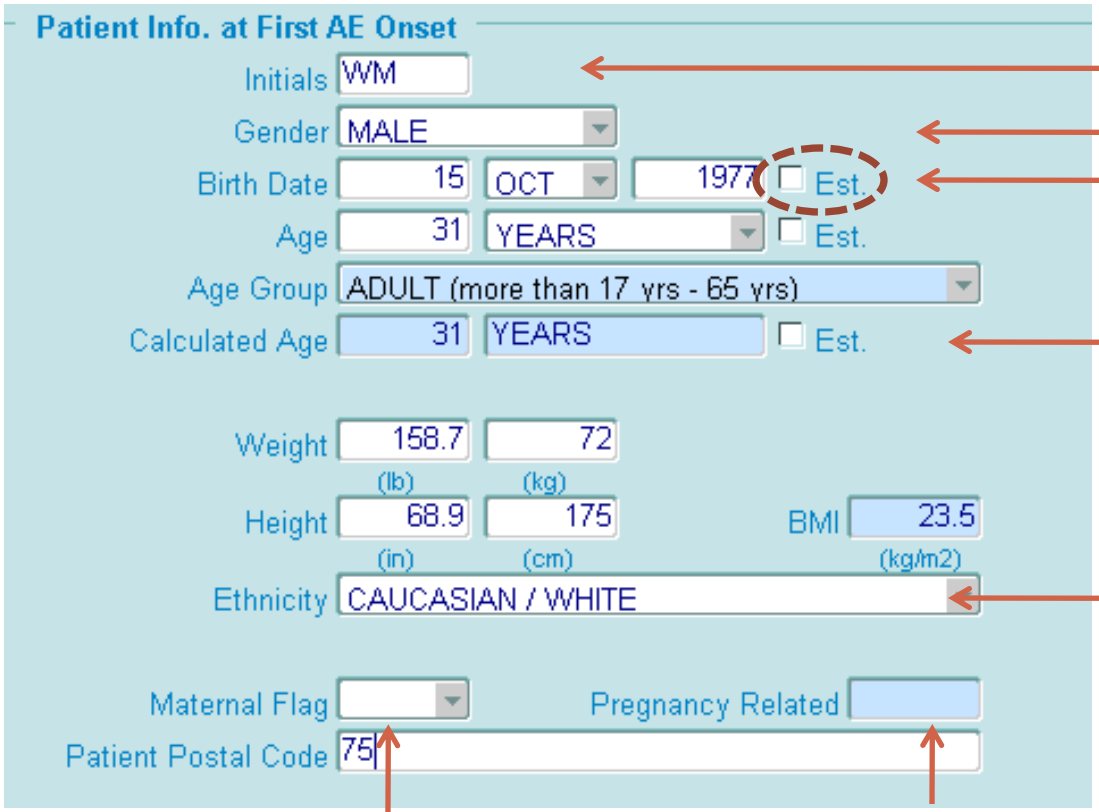
- **Summary Case, Legal Case**: left blank (but can be changed).
- **Event Country:** when country where event occurred and where it was reported are different.
- **External case ID:** Case ID from other reference.
- **Authority number:** Unique number assigned by Health Authority (reports from HA)
- **Design:** Blind/ single blind/ open/ double blind/ triple blind/ unknown (can be changed).
- **Phase:** I/II/III/IV

1) Report Screen (Cont..)



- **Study Type:** CTC, CT-NC, Compassionate use, Drug surveillance (PMS studies)
- **Study:** unique study ID (usually $ or % used to search appropriate study).
  On correct study selection: Study name and investigator auto filled.
- **EUDRACT:** Authorization number if study has a trial conducted in EU**.**
- **Design:** Blind/ single blind/ open/ double blind/ triple blind/ unknown (can be changed).
- **Phase:** I/II/III/IV

2) Patient Screen



Initials of first, middle and last name

M/F/unknown

partial DOB (year, or month and year and tick

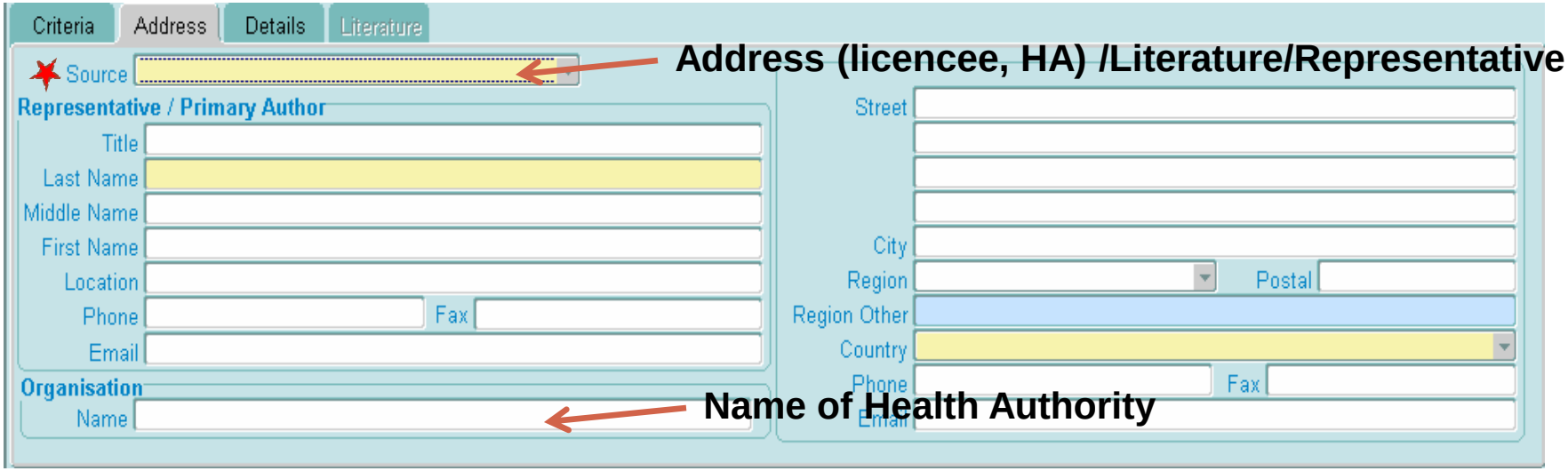
autopopulated using date of first AE and DOB (if both are entered)

Other:
free text: Hispanic/Black/ Asian

AE related to baby/ foetus/ placenta/ umbilical cord/ amniotic fluid

AE related to mother
(disabled if pregnancy is flagged in the initiate/report screen)

3) Reporter Details



❑ **Primary reporter**

Reporter most likely to have access to detailed information regarding drug experience

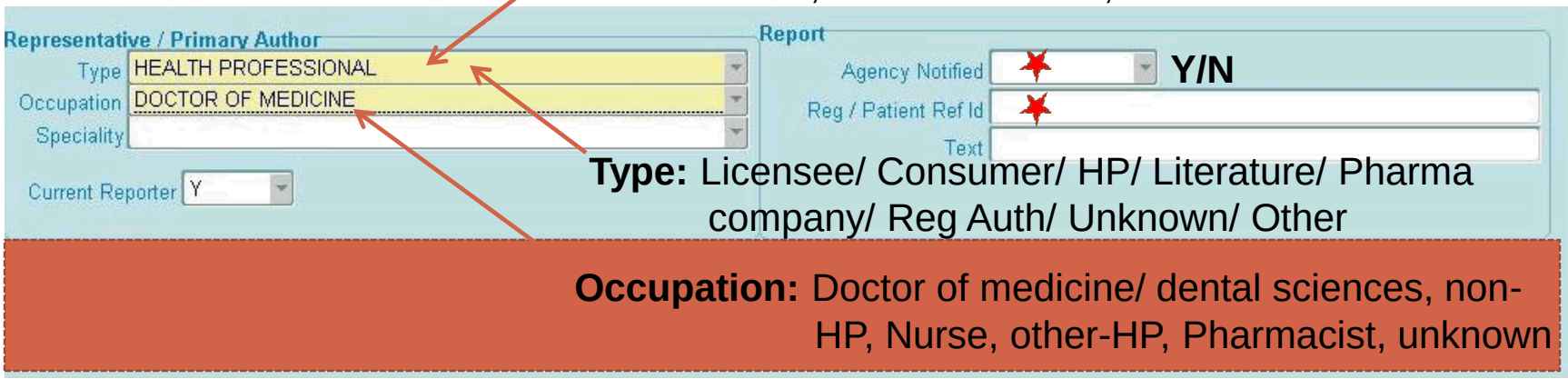
e.g. 1) patient reported event and a follow-up report is received from a doctor (doctor primary reporter).

2) nurse phones on behalf of doctor (enter the name of the doctor).

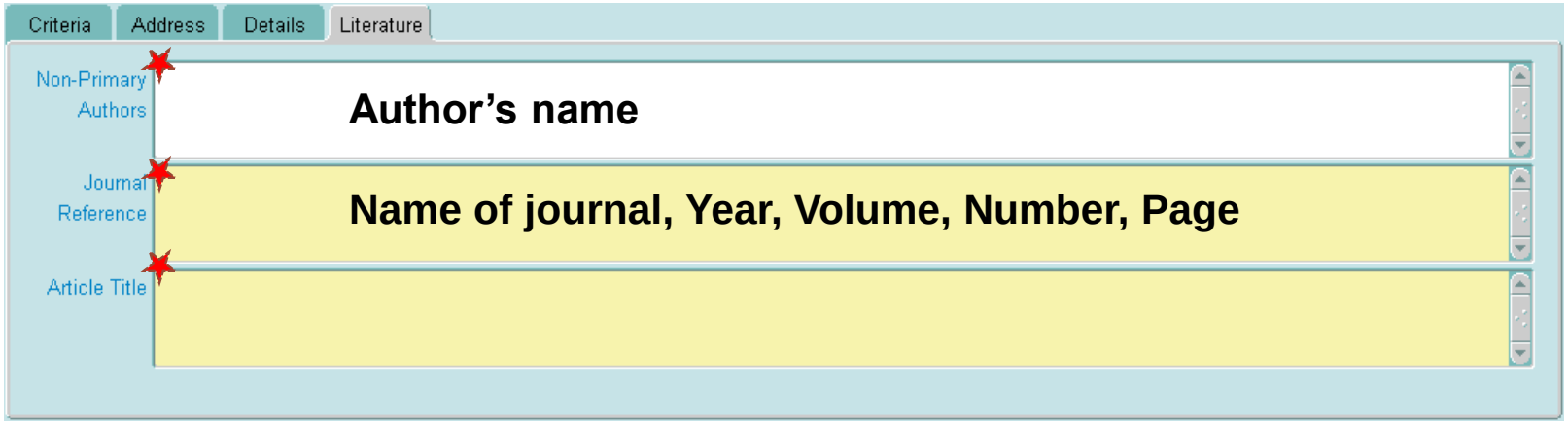
3) if **more than one doctor provide information** on an event, the doctor who treated the event (or if the latter has not provided the information then the doctor who proscribed the drug

❑ Primary reporter must be first in the list of the reporters (Resequence buttons should be used if necessary)

Not qualified health professionals:
Student doctor, student dentists, student vets

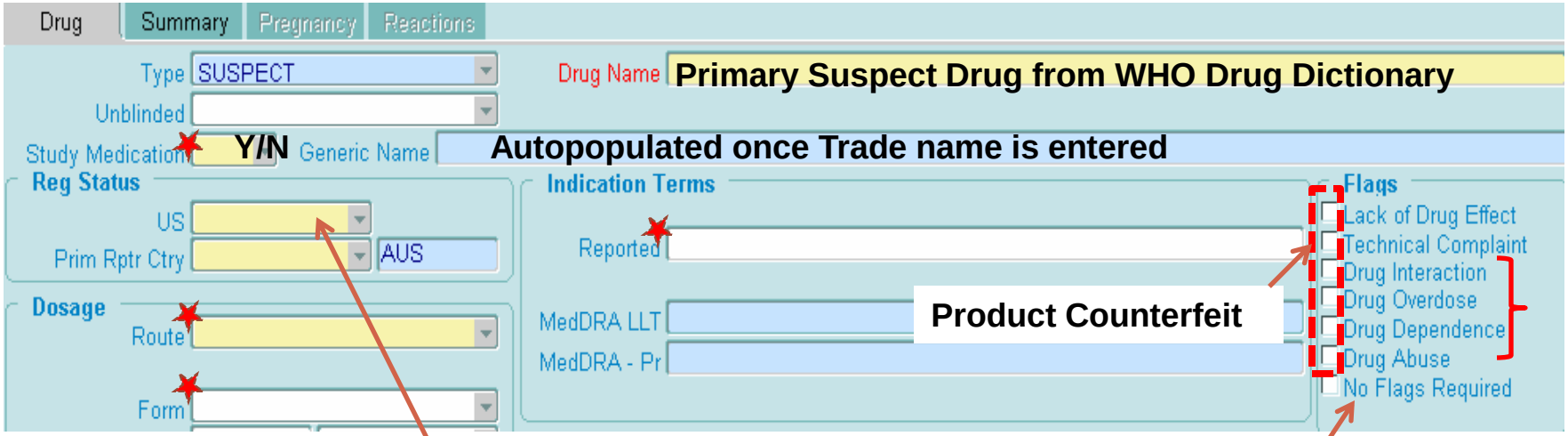


For Literature cases:



3) Drugs Details

- ❑ Information pertaining to **Suspect drug/ Concomitant drug/ Past drug.**
- ❑ Suspect drug should be primary drug.
- ❑ Drug name selected from WHO Drug Dictionary.
- ❑ Appropriate flag should be selected



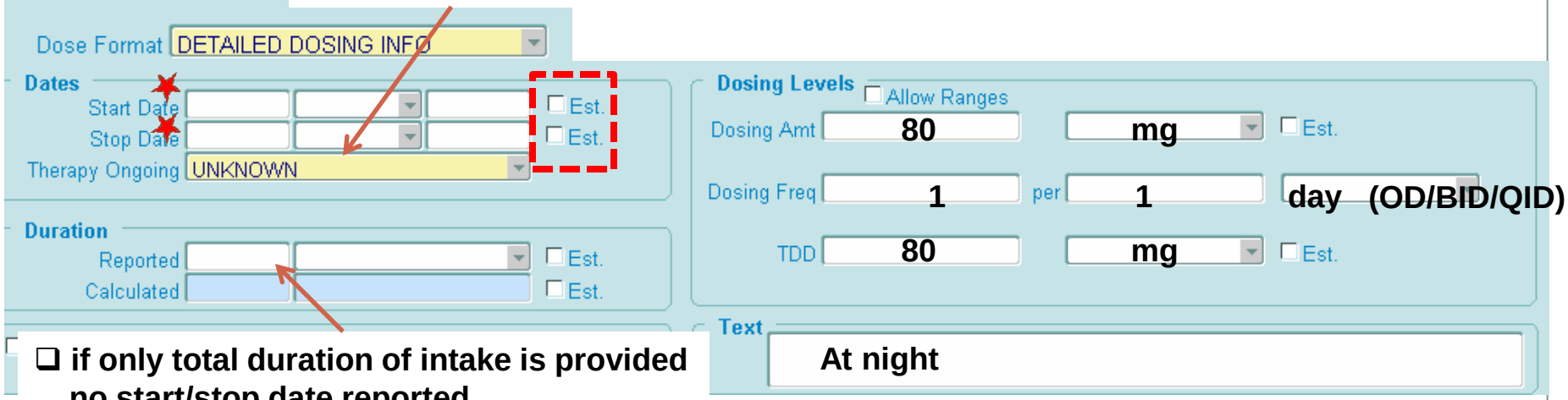
Study: IND number
Spontaneous: NDA

Normal scenario

- ❑ Drug indication enter as reported or “Drug use for unknown indication”.

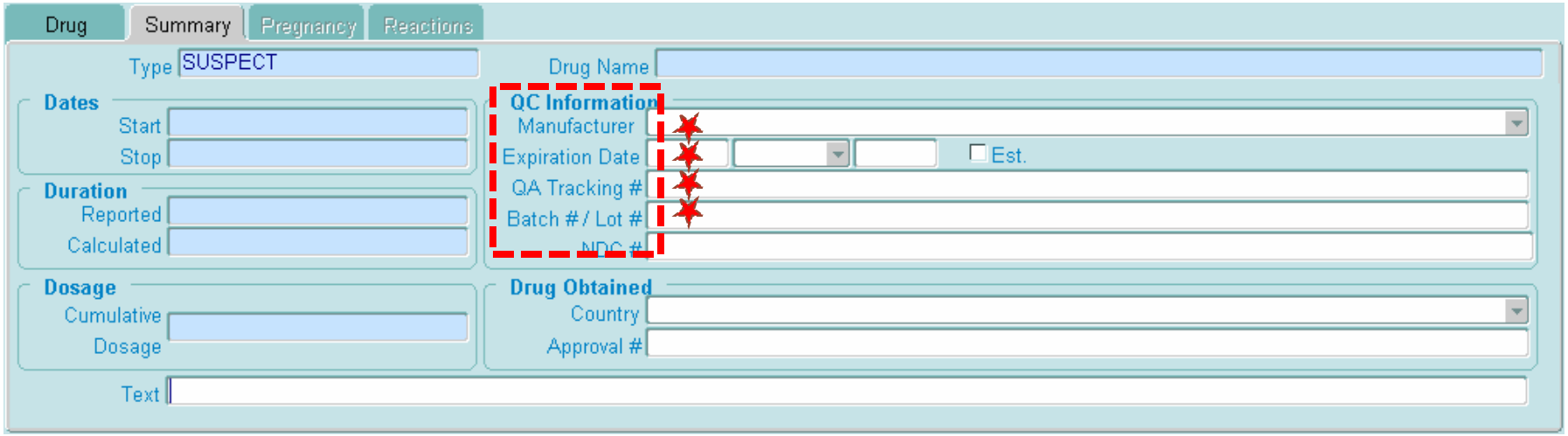
3) Drugs THERAPY Details

❑ if stop date is not provided: continued, unknown, N/a (suicide/ death cases)



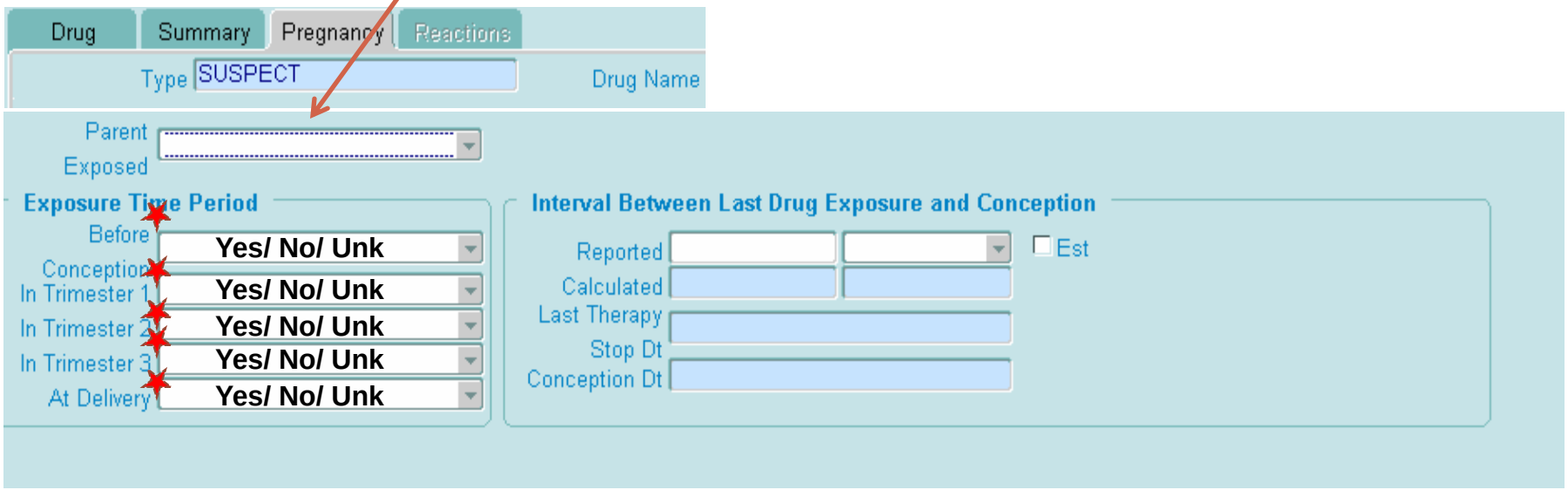
❑ if only total duration of intake is provided no start/stop date reported.

❑ If the drug flag is marked as Technical complaint/Product Counterfeit



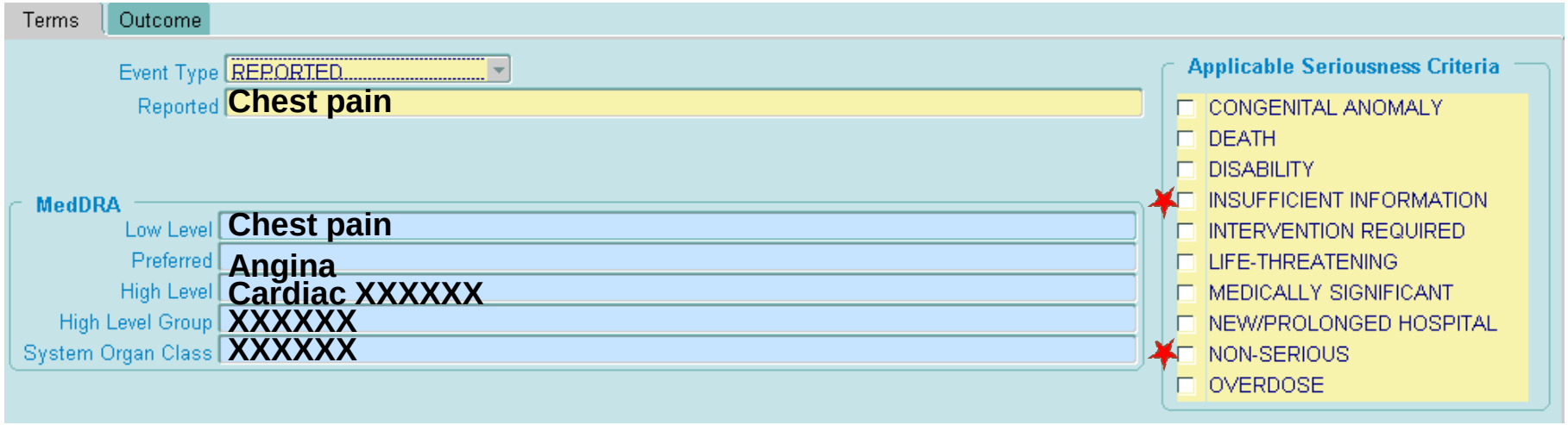
3) Drugs THERAPY Details (during pregnancy)

❑ **Mother/ Father (who consumed medicine)**



4) Adverse Event Details

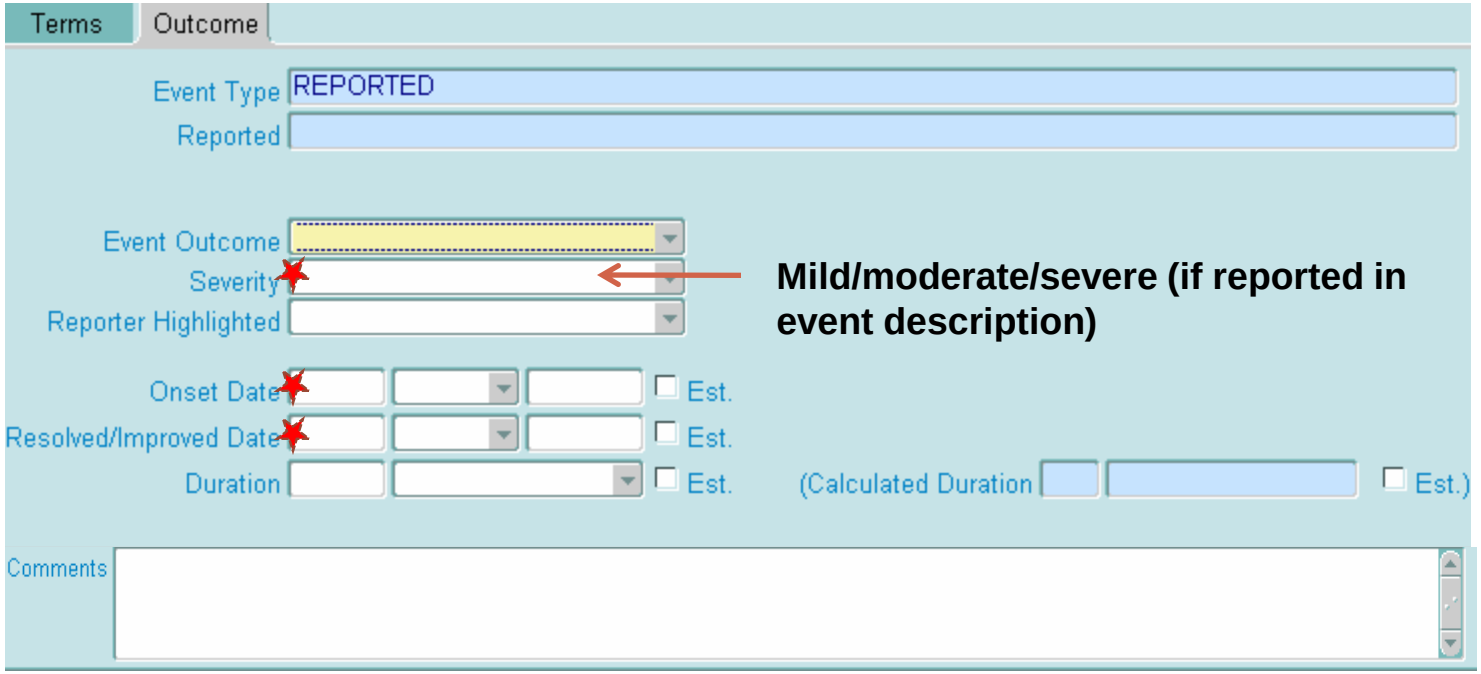
- ❑ **Report event as reported** (should not be change by self).
- ❑ **Link Reported term with appropriate LL/PT** (using MedDRA).
- ❑ Flag seriousness criteria as reported (for serious cases)
- ❑ Seriousness criteria flag can be changed (for non-serious/low cases)



FDA Designated Medical Events (DME)	
Still birth	Cerebral infarction
Torsades de pointes	Agranlocytosis
Seizures	Hemolytic anemia
Pancytopenia	Liver necrosis
Steven-Johnson syndrome	Hypoglycemia
Anaphylaxis	Ventricular fibrillation
Abortion	Cerebral hemorrage
Malignant hypertension	Bone marrow aplasia
Status epilepticus necrolysis	Toxic epidermal
Diffuse intravascular coagulation (DIC)	Hepatic encephalopathy
Acute liver failure	Dialysis
Acute respiratory failure	

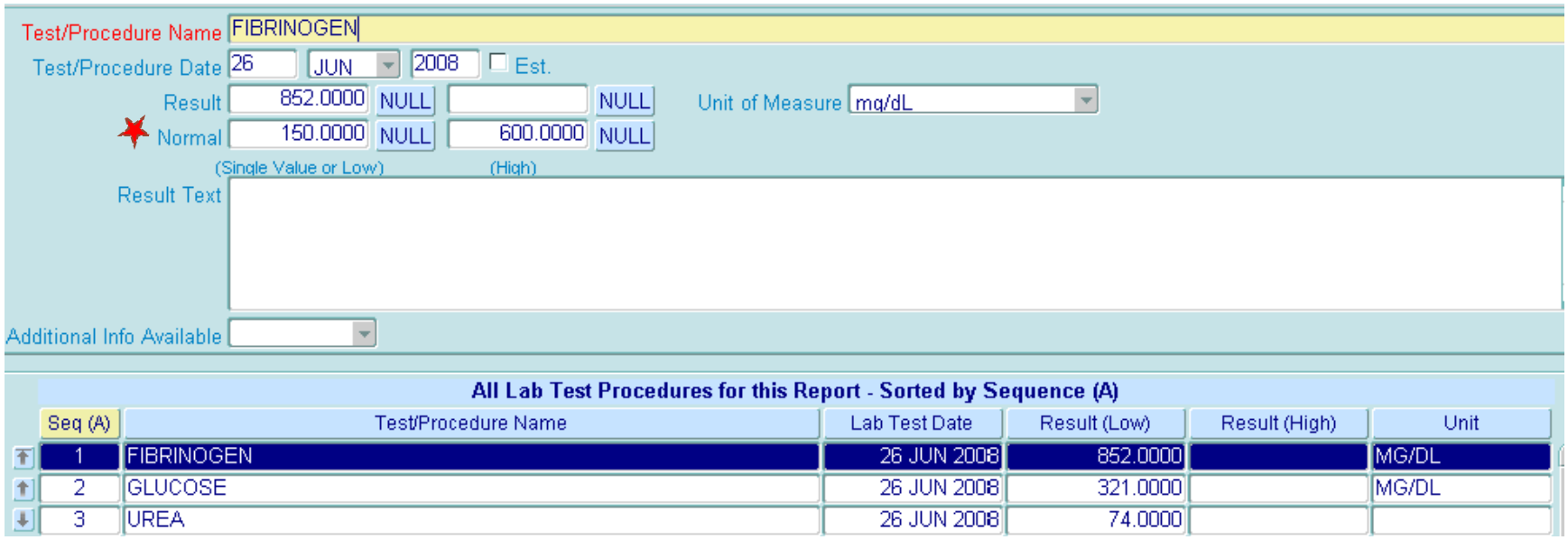
- List is short & provides only example of type of event generally **be considered potentially medically important (i.e. medically significant event)**.
- Careful consideration should be done in **upgrading the AE**.

- **Event outcome**:
  - Improved
  - Resolved
  - Resolved with squealae
  - Worsened
  - Unknown
  - Not provided
  - N/A (Death/ Pregnancy)



5&6) Medical History & Lab investigations

- ❑ Medical history and lab investigations should be in chronology.
- ❑ Most relevant MH and Lab investigation should be at the top.
- ❑ Normal Lab investigation could be added from a reference book (if not reported but important).
- ❑ Error in it's entry result in non-substantive error.



8) Narrative

Spontaneous Cases

- Narrative usually consists of 4 paragraphs
  - Introduction
  - Medical history & concomitant drugs
  - Main body
  - Causality & follow-up information

e.g. This spontaneous case received on DD/MM/YY via Reg Authority, was reported by a physician and concerns a 32 year old female (BMI) who experiences life threatening event of cerebral hemorrhage while taking XXXX for (drug indication).

The patient's medical history included …….. and was taking ……concomitanly (only relevant MH & concomitant medication)

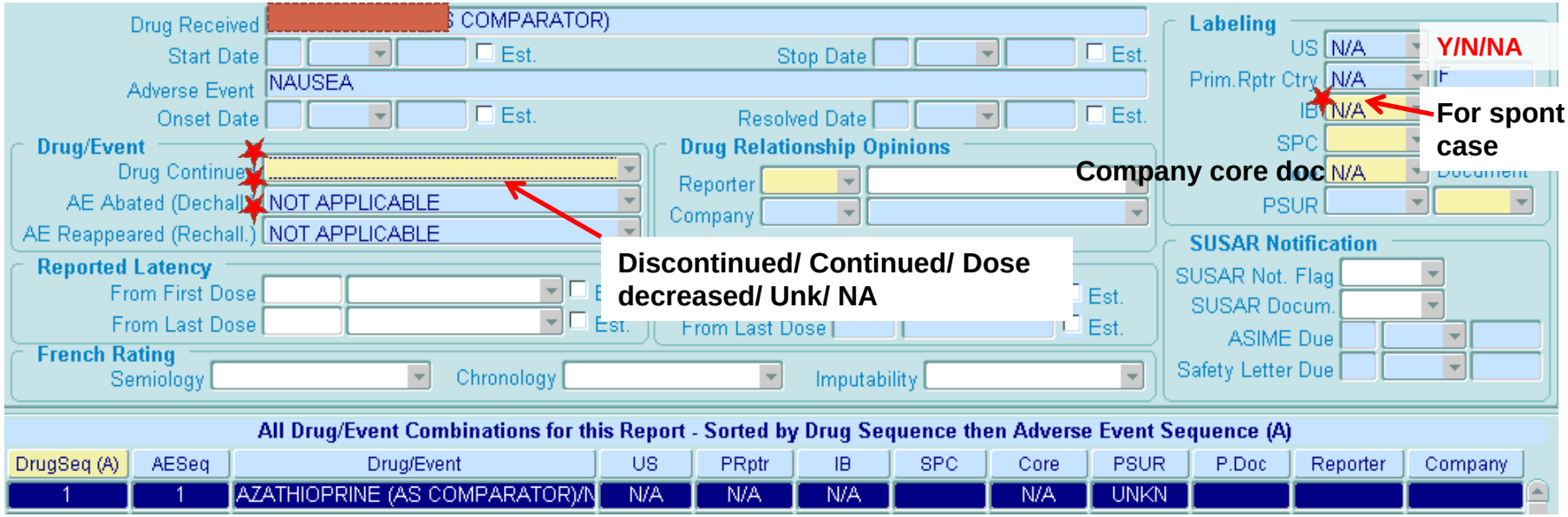
On DD/MM/YY, the patient started receiving oral paracetamol (200 mg tablet) at a dose of 200 mg thrice daily. Three days later, she experience high grade fever. The same day, lab test r

Study Reports

This clinical case was receive on DD/MM/YY and concerns a 52 year old female (CRTN) who was enrolled in the study "title" and developed pancytopenia.

8) Drug Event relationship

- ❑ Association b/w drug and event is established.
- ❑ Response of AE to Dechallenge and rechallenge.
- ❑ **Causality** (i.e. drug event relationship is established).
- ❑ **Labeling** as per expectedness of AE in reference safety information document.
- ❑ **SUSAR** (reported causality is related while the AE is unexpected in company ref doc.
- ❑ SUSARs qualify for expedited reporting (triage should be done carefully).
- ❑ **Reporter causality** capture as reported, however **company causality** is assessed by performing (Single case assessment).



Single case assessment (SCA) for Serious Spontaneous reports

- Single case assessment is **done to determine the Company drug/ event relationship** (i.e. expectedness).
- It consists of a **set of 10 questions**, which provide **numerical output** indicating the strength of association b/w the drug and AE.
- Scoring is based upon the amount and relevance of information that is available.
- It serves as a guideline for assigning the causality into **4 broad categories** (definite, probable, possible and unlikely).

Questions	Yes	No	Unkown
1) Are there previous conclusive report in this reaction?	+1	0	0
2) Did AE appear after the suspect drug was administered?	+2	-1	0
3) Did the AE improved when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4) Did the AE reappear when the drug was re-administered?	+2	-1	0
5) Are there alternative causes that could on their own cause AE?	-1	+2	0
6) Did the reaction reappear when a placebo was given?	-1	+1	0
7) Was the drug detected in blood (fluid) in conc known to be toxic?	+1	0	0
8) Was the reaction more severe on dose increase or vice versa?	+1	0	0
9) Did the patient had similar reaction to the similar drugs previously?	+1	0	0
10) Was the AE confirmed by any objective evidence?	+1	0	0

Interpreting the Naranjo

Score	Causality	Reporter drug relationship	Company Drug relationship	Drug Relationship
9+	Definite	N/Y/UNK	Y	Related
5-8	Probable	N/Y/UNK	Y	Related
1-4	Possible	Y/UNK	Y/UNK	Related
0 or less	Unlikely	N	N	Unrelated

Medical evaluation

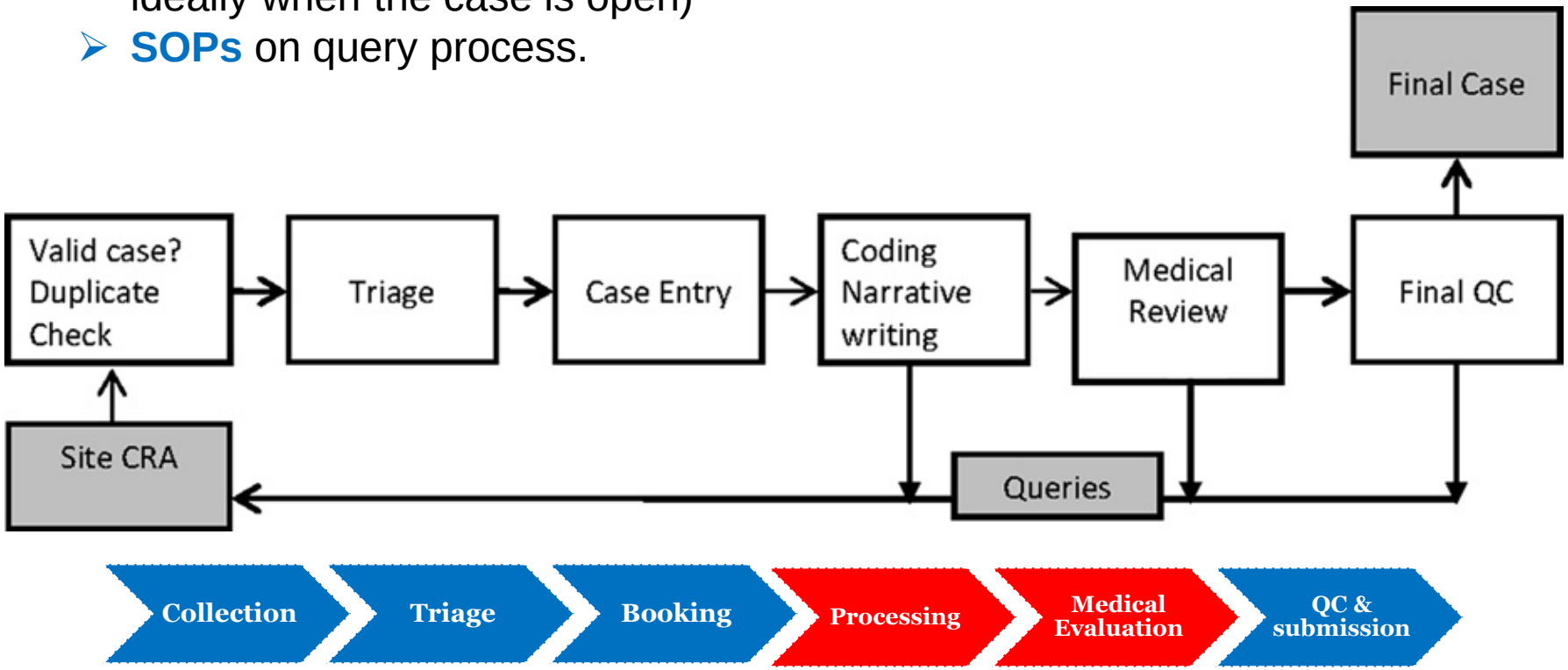
In medical evaluation, the HCP or DSP checks the:

- ❑ Appropriate **linkage of reporter AE** with the preferred term.
- ❑ The **labeling of the AE** against the reported events in the company labeling documents.
- ❑ **Seriousness and causality** assessment.
- ❑ **Alternative cause** of the ADR and CIOMS comments (if any).
- ❑ Medical history and additional information needed.
- ❑ Narrative (completeness, chronology and medical relevance).



Query or Additional Information

- Additional information is requested from the **affiliate** or **the investigator** for any discrepancy or support case information.
- Query can be sent during **case processing and medical review** (i.e ideally when the case is open)
- **SOPs** on query process.



Quality Check

- ICSRs are **randomly selected** for quality check.
- Ideally QC is done, when the ICSR/SAE report is ready for submission to the regulatory authority.
- Only important fields (which could leads to substantive correction) are checked against the source documents.
- Case after satisfactory QC is locked/closed and submitted to regulatory department and to licensee.

REPORT SCREEN	1	Report Origin
	2	Classification
	3	Local/External case ID
	4	Date received at company
	5	Medically confirmed
PATIENT SCREEN	6	Patient initials
	7	Patient gender
	8	Birth date / Age at time of Event
	9	Age Group
	10	Date of death if fatal outcome
REPORTER SCREEN	11	Last name/organisation
	12	Country
	13	Reg/Patient reference ID
	14	Reporter Type
SUSPECT ROCHE DRUG/COMPARATOR AND DRUG THERAPY	15	Drug selection/correct IND/NDA/formulation
	16	Dose, Frequency, Route and Therapy dates
	17	Lot number (if provided)
	18	Flags
CONCOMITANT MEDICATIONS	19	Drug names and therapy information
TEXT/NARRATIVE	20	Full narrative
ADVERSE EVENT SCREEN	21	Reported term
	22	Seriousness criteria
	23	Onset date
DRUG/EVENT SCREEN FOR SUSPECT AND COMPARATOR DRUGS	24	All relevant labels entered and correct
	25	Causality (Except for legal cases)

TYPES OF REPORTS RECEIVED AT THE PV CENTER:

- **Spontaneous Serious/ Non-serious case reports or SAE from clinical trials**:
  - Death
  - Lack of Effect (LOE)
  - Drug exposure during Pregnancy
  - Drug Counterfeit
  - Drug Interaction
  - Drug Dependence
  - Drug Overdose
  - Suicide
  - Drug Abuse
  - Medication Error (storage, prescribing, dispensing, administering)

Expedited Reporting

- ICSRs that involve a **serious and unlabelled event** (an event not described in the drug's labeling) that is **considered related to the use of the drug**.

- (Spontaneous reports are typically considered to have a positive causality, whereas a clinical trial case will typically be assessed for causality by the clinical trial investigator and/or the license holder.)

- In most countries, the **timeframe for reporting expedited cases** is **15 calendar days** from the time a drug company receives notification (referred to as "Day 0") of such a case .

- **Within clinical trials** such a cases is referred to as a **SUSAR** (a Suspected Unexpected Serious Adverse Reaction).

- If the **SUSAR involves an event that is life-threatening or fatal**, it may be subject to a **7-day "clock**". Cases that do not involve a serious, unlabelled event may be subject to non-expedited or periodic reporting.

Signal Detection

- The WHO defines a safety signal as: “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”.

- Usually **more than a single report is required to generate a signal**, depending upon the event and quality of the information available.

- **Data mining pharmacovigilance databases** is one approach that has become increasingly popular with the availability of extensive data sources and inexpensive computing resources.

- The data sources (databases) may be owned by a pharmaceutical company, a drug regulatory authority, or a large healthcare provider.

- Individual Case Safety Reports (**ICSRs**) in these databases are **retrieved and converted into structured format**, and **statistical methods** (usually a mathematical algorithm) are applied to calculate statistical measures of association.

Signal Detection (cont..)

- If the **statistical measure crosses an arbitrarily set threshold**, a signal is declared for a given drug associated with a given adverse event.

- All signals deemed worthy of investigation, require further analysis using all available data in an attempt to confirm or refute the signal.

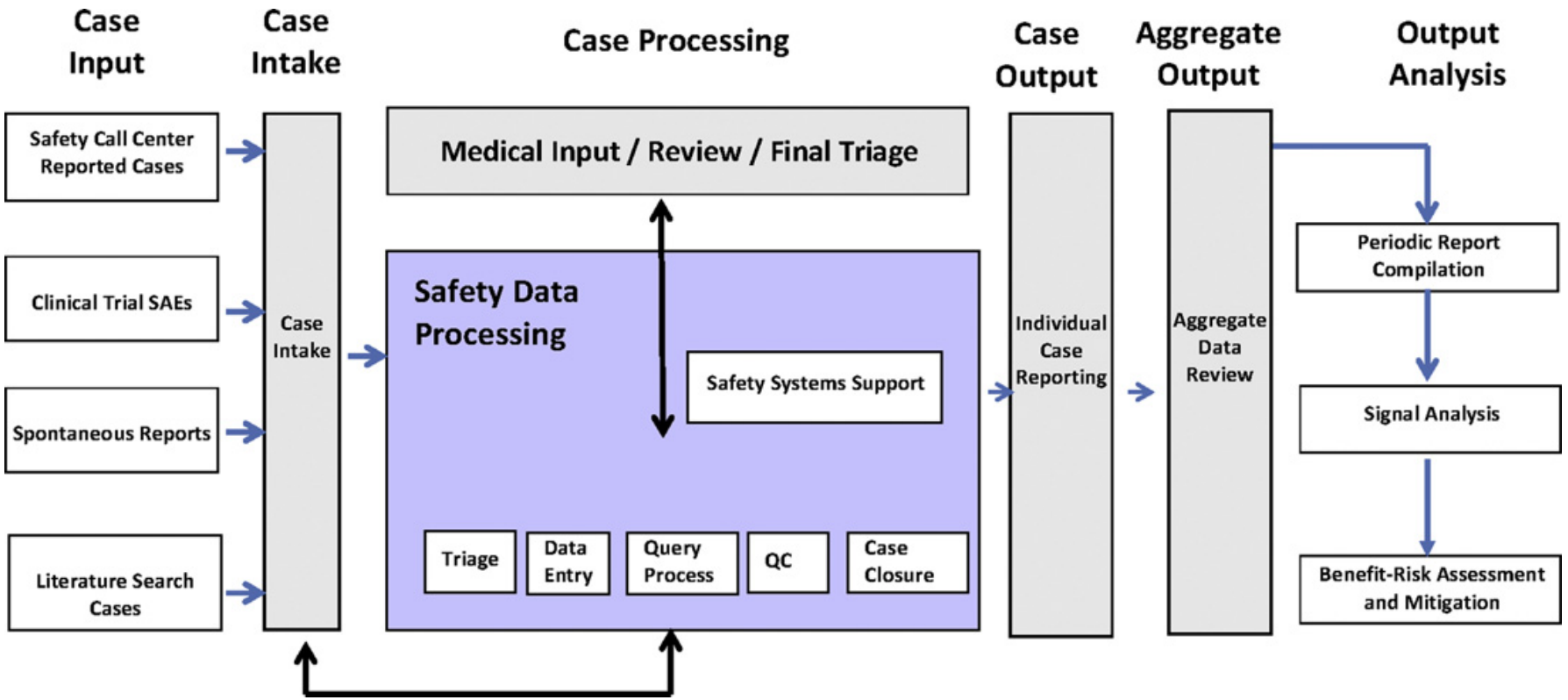
- If the analysis is inconclusive, additional data may be needed such as a post-marketing observational trial.

- Ideally, the goal of SD is to identify ADRs that were previously considered unexpected and to be able to provide guidance in the product's labeling.

  (**as to how to minimize the risk of using the drug in a given patient population**).

Summary


Collection
Triage
Booking
Processing
QC & submission
Output Analysis


Case Input
Case Intake
Case Processing
Case Output
Aggregate Output
Output Analysis
Safety Call Center Reported Cases
Clinical Trial SAEs
Spontaneous Reports
Literature Search Cases
Case Intake
Medical Input / Review / Final Triage
Safety Data Processing
Safety Systems Support
Triage
Data Entry
Query Process
QC
Case Closure
Individual Case Reporting
Aggregate Data Review
Periodic Report Compilation
Signal Analysis
Benefit-Risk Assessment and Mitigation

The Goal of AE reporting

When a drug is marketed it may be used in patient populations that were not:

- Studied during clinical trials (children, the elderly, pregnant women, patients with co-morbidities not found in the clinical trial population, etc.)

- A **different set of warnings**, precautions or contraindications (where the drug should not be used at all) for the product's labeling may be necessary in order to **maintain a positive risk/benefit profile** in all known populations using the drug.

Thank You For Your Attention !





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