Safety monitoring in clinical studies

- Proactive monitoring
- Timely detection and management of safety issues
- Interaction & communication with stakeholders.

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The speaker

- MD, EMBA, Post-graduate in pharmacology and pharmaceutical medicine.
- In charge of medical evaluation & risk management teams at big and small pharma (UCB, GSK Biologicals, Novartis Oncology, Basilea, Galderma): different therapeutic areas, investigational & marketed drugs.
- Last years, focused on investigational compounds (Phase I-II, mainly Phase III)

Disclaimer

- The views expressed reflect a personal opinion and not the opinion of the Company the speaker is working for or of a Company the speaker has worked for.

Content

- Set up a safety monitoring system at product level

- Flavour of FDA Guidance (Dec 2025)
  - «Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies”

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No “one fits all” approach

- Company
  - Size (established vs. start-up)
  - In-house vs. outsourced activities
  - Company’s internal structure, processes, staff, expertise
- Products
  - Innovative vs. generic products
  - Medicinal products, medical devices
  - In-house developed products vs. product after in-licensing/acquisition
- Clinical studies
  - Stage of development
  - Small studies (e.g. dose escalation studies, DDI, orphan drug) or large trials
  - All studies are open-label? Or also double-blind studies?
  - Multiple indications?
  - Different combinations?
- Co-sponsor or co-development partner?

Safety monitoring system (1/3)

- **Study level**
  - Study protocols / ICF:
    - Blood samples (PK) or pictures at time of occurrence of defined AEs?
    - Testing in case of suspected allergy?
    - Stopping rules?
    - Guidance for dose reduction?
    - Adverse Events of Special Interest?
  - ICSR review in PV database (SAE/SUSAR, pregnancy, AESI)
    - Staff trained on product & indication. Management of organ-specific ADRs; ensuring proper case documentation (e.g. standard questionnaires).
    - For “crucial cases” (e.g. DME-like): rapidly interact with Clinical Development; gather the info needed. Consider a “case definition” and -as applicable- perform case adjudication (e.g. hepatic).
  - Medical monitoring plan (owned by Clinical Development)
    - AEs, lab, vital signs, ECG
    - PV representative attending (part of) medical monitoring meetings? Or define how to escalate to PV.

Safety monitoring system (2/3)

- **Study level**
  - Safety monitoring plan
    - Define what and how to monitor to early detect potential safety issues
    - Individual cases or clusters of cases at study level, but also lab and other parameters
  - As applicable, study-specific DSMB / DMC

- **Product level**
  - Review aggregate data at program level (blinded), using common definitions / standards
  - Can include safety data received from Investigator-Initiated Studies or other studies

Safety monitoring system (3/3)

- Gather additional internal/external expertise as needed.
- **Escalation** / **Governance** as described in company procedures. For instance:
  - ICSR review, medical monitoring, new non-clinical data, DDI, …
  - ⬇
  - Safety Surveillance Team (product level)
  - ⬇
  - Benefit-Risk Team (product level)
  - ⬇
  - Governance body at therapeutic area level (if existing)
  - ⬇
  - Safety Board + CMO
- **Partner management**:
  - e.g. Joint safety assessment committee (Charter)
- For ongoing double-blind studies
  - Possibility to ask IDMC to look into a potential topic identified or to refer the matter to an internal body that is not involved in the conduct of the study?

Surveillance at product level

- Describe in a procedural document; e.g. Charter
- Who is involved in (PV, Biostats? Clinical Development? Epi?)
- Periodicity
- What to look into
- Which outputs to use from clinical database
  - Preferably via a central database that is regularly updated with data from all completed and ongoing clinical studies
  - Via tools like Cognos, Spotfire or via specific outputs.
  - Consider to group/pool studies as applicable
- Develop user-friendly tables/figures that rapidly provide a view
- Be aware of limitations (cleaning, coding)
- Close interactions with stakeholders
- Low suspicion treshold during early development phase
  - Low number of patients might require a « leave no stone unturned » approach

Fictive example

Topic	Frequency
Fatal TEAEs, SUSARs, SAE AESI / Designated Medical Events ICSRs with product quality issue, if any	Weekly
TEAEs leading to dose reduction of IMP TEAEs leading to dose reduction of Standard of Care SoC (oncology) TEAEs leading to temporary discontinuation of IMP or SoC TEAEs leading to permanant discontinuation of IMP (or SoC) Aggregate view of SAEs Literature (including epi, non-clinical, and therapeutic class)	Monthly
All safety data (non-serious TEAEs, lab, ECG parameters)	3-monthly
Reference Safety Information for comparator; Product Information for therapeutic class	6-monthly

What to focus on? Events under monitoring.

- Establish a list of topics under monitoring based on
  - Data on molecules with a similar Mode of Action or of the same therapeutic class
  - Existing data on IMP (e.g. IB, D-RMP, Benefit-Risk document), keeping in mind that a study might have more than one IMP
  - Non-clinical data
  - Based on previous clinical studies:
    - important identified / potential risks
    - Non-important risks with but impact on exposure to IMP or SoC
  - Designated Medical Event list or equivalent company list

- For each topic, define how to identify reports in an automated way across the development program:
  - Use existing Standardized MedDRA Queries (SMQ)
  - Or create appropriate search strategy (ideally to be used for other products too), using MedDRA PTs from different SOCs (e.g. Investigations)
  - For certain type of events, include laboratory anomalies in the search strategy (regardless whether reported as TEAE)
    - E.g: hepatotoxicity, nephrotoxicity, blood dyscrasias

Back-ground (epidemiological) data

- For (relevant) safety concerns, gather back-ground data (e.g. incidence, severity, outcome, risk factors)
- Data sources: e.g. epidemiological databases, claims databases, registries, in-house or external studies with other compounds in the same indication
- Not always easy to retrieve data from a population that is similar to the population that is being studied.
- Quite often one ends up with a range.
- Observed-Expected (0-E) analyses might become tricky

- Might be tricky to compare to a “similar study”, even when very comparable baseline patient characteristics (which are quite often looked into from an efficacy point of view).
  - For the safety concern of interest, identify the major risk factors
  - Liaise with Biostatistics to see whether these major risk factors have comparable incidences in both studies and study arms.

User-friendly tables/figures

- Interact with dedicated staff and explain what you like to see.

- Visual presentation that shows
  - Proportion of SAEs vs. AEs
  - The outcome
  - Severity grades

- Lab values:
  - Consider presentating the quartiles or every 10th percentile

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SAE expedited reporting

Not reportable

Reportable

May be reportable as aggegate data

	Expected	Unexpected
Not related		
Related	SAR	SUSAR

Dec 2025 Guidance

	Expected	Unexpected
Not related	**Anticipated events**: expedite if increased frequency (aggregate)	
Related	If increased occurrence (aggregate)	Uncommon and known to be strongly associated with drug exposure (e.g. SJS) Uncommon in the population exposed (e.g. heart valve lesions in young adults)

Events that can be expedited without aggregate analyses

- 1. **Individual occurrences**: uncommon and known to be strongly associated with drug exposure (e.g., angioedema, agranulocytosis, hepatic injury, anaphylaxis, SJS).
  - The occurrence of even one case of such an SAE must be reported as IND safety report.
  - The blind should be broken (e.g. impact on informed consent).

- 2. One or more occurrences: not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture, heart valve lesions in young adults, intussusception in healthy infants)
  - A single case may be persuasive enough to report (e.g. strong temporal association, + rechallenge).
  - Often, > 1 case would be needed (from one or multiple studies) to determine that there is a reasonable possibility that the drug caused the event.
  - Such events should be unblinded

Events that require aggregate analyses

- 1. Events anticipated to occur in the study population, independent of drug exposure
  - Common events related to the underlying disease or condition under investigation
  - Common events in a population regardless of the underlying condition being studied
  - Known to occur with background regimen drugs.
  - No expedited IND safety reporting as individual ICSR.
  - Perform aggregate analysis and consider all relevant drug development data.
  - Medical concept associated with an SAE may be reflected by a number of different PTs.
- 2. Increased occurrence of an expected serious suspected adverse reaction
  - Must report any clinically important increased rate (compared to protocol or IB).
  - Judgment based on e.g. study population, nature and seriousness, magnitude of the increased incidence.
  - Systematic safety surveillance process to monitor the rate and protect the integrity of a blinded trial

Other Reporting Requirements

- Findings that suggest a significant risk in humans exposed to the drug.
- A. Findings from other studies: ongoing or completed clinical studies, pooled data, and epidemiological studies.
- B. Review and evaluate safety information to determine any newly identified significant risk.
  - Animal or in vitro studies, scientific literature (e.g. unpublished reports of which the sponsor becomes aware), presentations at professional or scientific meetings, reports from foreign regulatory authorities,…..

- Purposes:
  - Decide whether the information meets the criteria for expedited reporting.
  - Regularly evaluate all accumulating data to update safety information (IB, ICF, protocol) and to identify new safety signals.
  - Take steps to protect participants.

Safety Surveillance Plan (SSP)

- Review of SAEs and important safety data (e.g. related Aes) with unblinding if necessary.
  - A list of anticipated SAEs for the study population.
  - A plan to monitor the incidences of SAEs that require aggregate reporting.
    - Anticipated SAEs (both prespecified and those not on the anticipated SAE list)
    - Expected serious suspected adverse reactions.
  - If using a trigger a trigger approach to unblind: specify the predicted rates of anticipated SAEs and their basis.
  - The frequency and approach of aggregate safety data reviews.
  - Pre-planned assessments of the trial and program safety database: e.g. at completion of trial, when safety information from trials of other drugs in the same class, or when safety-relevant info (e.g., pharmacology, toxicology, genetics).
  - Methods that may be used to evaluate events: graphical, tabular, or statistical approaches.
  - Unblinding practices and controls and processes for maintaining trial integrity.
- Evaluate the safety surveillance plan as the development program progresses to determine to update the plan .
- The plan should be maintained by the sponsor and must be available for FDA inspection.
- Roles and responsibilities for review, analysis and decision-making of IND safety reporting.

Who will review aggregate data?

- Individual or a group of individuals
  - review the unblinded accumulating safety information in a program
  - make recommendation whether the safety information must be reported.
- There can be more than one entity to evaluate all SAEs; e.g.
  - an entity to assess individual cases or a small number of not anticipated events;
  - a different entity assessing aggregate adverse events;

- Knowledge about the drug; the disease treated, and the study population (background rates).
- Qualified by training and experience to make clinical judgments about the safety of the drug.
- Additional expertise may be warranted when new safety concern (e.g. renal toxicity).

- Firewall procedures in place to ensure blinding.
  - If a firewalled external entity other than the IDMC/DMC looks at aggregate data, it should have access only to the unblinded data necessary to conduct the safety review (no access to study endpoints, efficacy data).

If aggregate analysis is done by IDMC

- Review accumulating unblinded safety data to assess incidence of anticipated SAEs and expected SARs by treatment arm.
- Accumulating information from the drug development program, not just the specific trial.
- Should be aware of preclinical and early clinical data that bears on safety issues.
- If the entity identifies an imbalance for an anticipated SAE OR a rate of an SARs in the treatment arm above what is expected: recommendation to Sponsor staff assigned to review unblinded data to determine if an IND safety report is appropriate.
- Periodic aggregate analysis:
  - at regular intervals (e.g., every 6 months, or more or less frequently as appropriate).
  - or based on volume of safety data collected OR participant accrual (e.g. 25 %)
  - Other factors (e.g. experience, the condition, study population, enrollment rates)
- The frequency may be modified as needed.
- An imbalance might be determined not to require an IND safety report but could lead to more frequent monitoring.

Anticipated SAEs

- Predicted rate :
  - based on information that is applicable to the specific study population.
  - Use all available data (e.g. placebo databases, historical data, literature, epidemiological data, electronic health records, disease registries).
  - Not expected that all anticipated SAEs, particularly for less common anticipated SAEs, would be prespecified in the SSP.
- When accurate population-based rates can be calculated: a precise trigger for unblinding can be used.
- Unblinding criteria based on comparison of predicted rate and observed blinded rate.
  - If the rate in the blinded pooled groups exceeds the predicted rate by more than a minor difference): then unblinded to determine whether IND safety reporting criteria are met.
  - Clinical judgment should be incorporated: e.g. seasonally higher rate of pneumonia.

CONCLUSIONS

- Team work
- Start with what is really needed for that product.
- Use outputs that rapidly give you a view.
- Monitor whether safety profile and reported incidences are as expected and whether current risk minimisation measures seem effective
- Cave impact on Standard of Care (oncology)
- As needed, bring in additional expertise and escalate
- Document what is to be done and what was done

THANK YOU FOR YOUR ATTENTION!

QUESTIONS?

Unblinding trigger approach

- Recommended if there is no external entity to conduct periodic unblinded reviews.

- FDA acknowledges that serious suspected ADRs may be unblinded at the site level if knowledge of the treatment received is assessed as necessary for the medical management of the participant.
- To address sponsor concerns about unblinding large numbers of participants' treatment to investigators when submitting aggregate reports, FDA recommends sending only the narrative summary portion of the IND safety report to all participating investigators, without the individual unblinded case safety reports that are summarized in the narrative summary report, to meet the requirement for a sponsor to notify all participating investigators in an IND safety report of potential serious risks.

Expected Serious Suspected Adverse Reactions

- Trigger to unblind is based on rates listed in the protocol or IB;
  - take into account whether the events being monitored could occur in the control group.
- Have processes for comparing the rates of expected serious suspected adverse reactions to the rates listed in the protocol or IB to determine whether there is a clinically important increased rate of occurrence that must be reported.