



The principles of clinical safety

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The principles of clinical safety

- Governing laws
- Definitions
- Overall responsibilities
- Types of clinical data
- Collection & processing of reports from interventional CTs
- Expert review groups EU - USA
- Expedited Reporting



Principles of clinical safety – Governing laws

USA - Code of Federal Regulations (CFR)

Title 21 - Foods and Drugs

- Chapter I - Food and Drug Administration
 - Subchapter D - Drugs for Human Use
 - Subchapter F - Biologics
- Part 312 - Investigational New Drug Application
 - 21 CFR 312.32 - IND Safety Reports
 - 21 CFR 312.33 - Annual Reports
 - Subpart D - Responsibilities of sponsors and investigators - starting with 21 CFR 312.50
 - informing investigators, Investigator brochures, etc.
 - Good Clinical Practice



Principles of clinical safety – Governing laws

EU - Clinical trial directive

Requirements for the conduct of clinical trials in the EU are provided for in ["Directive 2001/20/EC of the European Parliament and of the Council"](#)

The Clinical Trials Directive is concretised further by ["Commission Directive 2005/28/EC of 8 April 2005"](#)

New Clinical trial Regulation EU N° 536/2014 to become effective in 2018



Principles of clinical safety – Governing laws

EU - Clinical trial directive

The goal of [Clinical Trial Regulation EU No. 536/2014](#) is to create an environment that is favourable to conducting clinical trials in the EU, with the highest standards of **safety** for participants and increased **transparency** of trial information. The Regulation will require:

- **consistent rules** for conducting clinical trials
- information on the authorisation, conduct and results of each clinical trial carried out in the EU to be **publicly available**.
- This will **increase the efficiency** of all trials and help **avoiding unnecessary duplication**



Principles of clinical safety – definitions

Interventional clinical trial (Phase I to IV)

US (ClinicalTrial.Gov): A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions



Principles of clinical safety – definitions

Sponsor

Defined in EC Directive 2001/20/EC as an ‘individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial’

Investigator

The individual who is responsible and accountable for conducting the clinical trial. The PI assumes full responsibility for the treatment and evaluation of human subjects, and for the integrity of the research data and results



Principles of clinical safety – definitions

IMP (Investigational Medicinal product)

Pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or **assembled (formulated or packaged) in a way different** from the authorized form, or when **used for an unauthorized indication**, or when used to **gain further information about the authorized form**



Principles of clinical safety – definitions

Non IMP (Investigational Medicinal product)

Medicinal products that do not fall within the definition of IMP (e.g. used as a concomitant medication for preventive, diagnostic and therapeutic reasons)

IND (US specific)

Investigational New Drug application: a request for authorization from the FDA to administer an investigational drug or biological product to humans



Principles of clinical safety – definitions

Serious AE or ADR (ICH and FDA)

- results in death
- life-threatening
- requires or prolongs inpatient hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other important medical events that, based upon appropriate medical judgment, may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the above outcomes are also serious



Principles of clinical safety – definitions

Unexpected Adverse Drug Reaction (FDA)

- An ADR, the nature or severity of which is not consistent with the applicable product information (relevant source documentation) (ICH; FDA 312.32)
- Unexpected/expected from the perspective of what has been observed, not on the basis of what might be anticipated from the pharmacological properties of the product. (FDA 312.32 and 314.80)
- Not listed in current product labeling. Includes events that may be pathophysiologically or symptomatically related to a listed event, but differ due to greater severity or specificity. (FDA 314.80)



Principles of clinical safety – definitions

Minimum Information for a Report

- Identifiable subject (e.g trial number)
- Identifiable reporting source
- Adverse event
- Suspect investigational medicinal product

Minimum Information for a SUSAR

- Identifiable subject (e.g trial number)
- Identifiable reporting source
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
- Suspect investigational medicinal product



Principles of clinical safety – overall responsibilities

Study sponsor

- Selecting the investigator(s)
- Providing the investigator with sufficient information to conduct the trial
- Ensure proper monitoring
- Ensure all necessary ethic review(s) and approval(s) are obtained
- Preparing and submitting clinical trial application and amendments



Principles of clinical safety – overall responsibilities

Study sponsor

- Ensuring compliance with labelling, reporting and record-keeping requirements
- Ensuring that any reviewing ethic boards and regulatory agencies are promptly informed of any significant new information
- Refraining from engaging in promotional activities and other prohibited activities



Principles of clinical safety – overall responsibilities

Study sponsor

- Ensuring that the study is conducted in accordance with Good Clinical Practice (GCP)
- Define specific requirements/methods for collecting, recording and notifying AEs in the trial including reconciliation with clinical DB
- Define which events should be recorded and where (clinical and/or safety DB)
- Ensure expedited and periodic reporting to CA/EC & Investigators



Principles of clinical safety – overall responsibilities

Study investigator

- Conducting the study i.e overseeing the administration of the test product(s) to the subjects
- Protecting the rights, safety and welfare of subjects in the study
- Ensuring that informed consent is obtained from subjects



Principles of clinical safety – overall responsibilities

Study investigator

- Ensuring that the trial is conducted in accordance with the signed agreement and the investigational plan
- Controlling the product(s) under investigation
- Ensuring proper record keeping and reporting requirements are met



Clinical Safety - types of clinical safety data

Solicited adverse events (reactogenicity): local and general

Unsolicited adverse events (excluding serious)

Serious adverse events

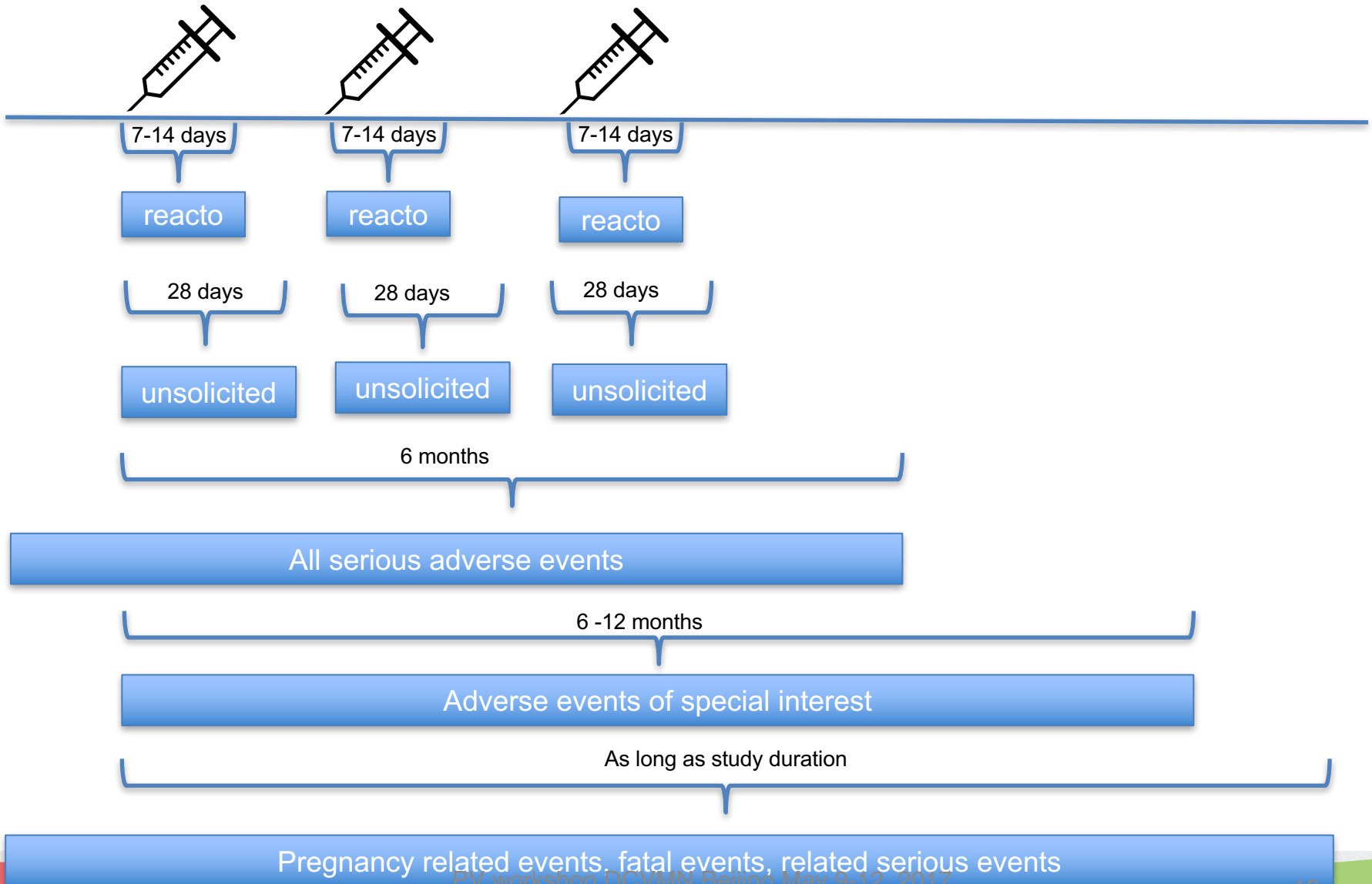
Fatal events

Pregnancy related events

Adverse events of special interest



Clinical Safety - collection of safety data





Principles of clinical safety – collection and evaluation of ICSRs

COLLECTION OF ICRS - Investigators/Sites

- Assessment of event seriousness
- Assessment of causality
- Must report SAEs, ESIs and pregnancies to the sponsor according to the defined timelines (SAEs: immediately and not later than 24 hours)
- Use of SAE/pregnancy specific forms either electronic or paper based as defined in SMP/protocol
- Follow-up of SAEs, ESIs and pregnancies
- Proper record management of study files



Principles of clinical safety – collection, evaluation and reporting of ICSRs

COLLECTION OF ICRS - Sponsors

- Must have in place a system to collect ICSRs
- Responsible for evaluation and assessment of information
- Causality assessment
- Unblinding of SUSARs & emergency unblinding
- Follow-up queries to the sites/investigators
- Expedited reporting of SUSARs to CA and EC
- Informing investigators



Principles of clinical safety – collection, evaluation and reporting of ICSRs

- Assessment of expectedness in the light of the reference safety information (RSI) for the product under investigation
 - According to the SmPC for a product with a marketing authorisation
 - According to the IB (Investigational Brochure) for investigational medicinal product
- Reconciliation of SAEs (define frequency)
- End of study unblinding



Principles of clinical safety – collection and evaluation of ICSRs

Sponsors – aspects to consider

- ✓ Importance of written procedures
- ✓ Choice of clinical and safety data databases: from the most 'primitive' to the most sophisticated tools.
- ✓ Appropriate training of investigators
- ✓ Appropriate monitoring of trials
- ✓ Ensure that all vendors (CROs) involved in the process are appropriately qualified to perform the delegated tasks
- ✓ Safety data in clinical trial master file
- ✓ Safety data in clinical study report



Principles of clinical safety – Expert Reviews

EU - DSMB: Data and Safety Monitoring Board

- Independent group of experts that advises the sponsor and investigators
- Provide expertise and recommendations
- Should review each protocol for major concerns prior to implementation
- Must maintain confidentiality of internal discussions and activities
- DSMB charter



Principles of clinical safety – Expert Reviews

Usually required for multi site and phase III studies and in the following situations

- When trial is intended to provide definitive information about effectiveness and/or safety
- If there are prior data to suggest that the intervention being studied has the potential to induce potentially unacceptable toxicity
- If the trial is evaluating mortality or another major endpoint such that inferiority of one treatment arm has safety as well as effectiveness implications



Principles of clinical safety – Group Expert Reviews

Items usually reviewed by a DSMB:

- Interim/cumulative data for evidence of study-related adverse events;
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines, if appropriate;
- Data quality, completeness, and timeliness
- Performance of individual centers;
- Adequacy of compliance with goals for recruitment and retention, including those related to the participation of women and minorities



Principles of clinical safety – Group Expert Reviews

- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study



Principles of clinical safety – Group Expert Reviews

Recommendations of a DSMB could include:

- Modifications of the study protocol based upon the review of the safety data;
- Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance or rate of enrollment;
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines



Principles of clinical safety – Group Expert Reviews

- Optional approaches for sponsor and investigators to consider when the DSMB determines that the incidence of primary study outcomes is substantially less than expected such as recommendations to increase the number of trial centers or extend the recruitment period; and,
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious



Principles of clinical safety – Group Expert Reviews

FDA –Draft guidance on proposed changes on safety surveillance and reporting for clinical trials

- The aim of this draft guidance is to explain how sponsors should develop a systematic approach to IND safety reporting, in particular for situations where there are multiple studies of the same experimental product. The rationale is for sponsors and FDA is to detect and evaluate, as early as possible, SUSARs and clinically important increased rates of known SAEs.
- Information in this document is non-binding



Principles of clinical safety – Group Expert Reviews

- The document then summarizes the IND safety reporting requirements (21CFR312.32, 310.305, 314.80, 600.80 and 606.170). This draft guidance is a fine, concise review of the basic safety reporting requirements and is worth the read and review.
- Applicable to **experimental drugs**, even marketed ones undergoing new indications



Principles of clinical safety – Aggregate reporting

Five major themes

- Use of a **Safety Assessment Committee**
- Performance of aggregate analyses to compare AE rates across treatment groups
- Planned unblinding of safety data
- Reporting thresholds for IND safety reporting
- Development of a **Safety Surveillance Plan**



Principles of clinical safety – FDA specifics

Safety surveillance plan should describe processes and procedures for assessing serious adverse events and other important safety information and address the following:

- Determining needed expertise for the safety assessment committee (e.g., cardiologists, hepatologists, clinical pharmacologists)
- Planning for the safety assessment committee's review of SAEs and other important safety information (e.g., nonclinical, epidemiologic, observational data) as needed
- Ensuring that all serious adverse events from all ongoing studies and other important safety information are provided to the safety assessment committee for routine reviews and for timely ad hoc reviews as needed
- Unblinding practices



Principles of clinical safety – FDA specifics

The safety surveillance plan must be maintained by the sponsor and available for FDA inspections.

FDA recommendation: sponsors should submit a portion of the safety surveillance plan to FDA before initiating phase II or III studies (mainly list of anticipated SAEs and previously recognised SARs and guiding principles for periodic aggregate safety reviews).



Principles of clinical safety – Expedited reporting

FDA - IND requirements (21 CFR 312.32)

Format and means

- Medwatch (FDA 3500A)
- CIOMS usually accepted
- Need a submission serial number (from FDA)
- No gateway yet – usually done by local regulatory contact person



Principles of clinical safety – Expedited reporting

What needs to be reported?

Events that are serious, unexpected and related i.e

- Single occurrence of event that is uncommon, and known to be associated with drug exposure
- One or more occurrences of event that is not commonly associated with drug exposure, but is otherwise uncommon in the exposed population
- Aggregate analysis of specific events observed in a trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group



Principles of clinical safety – Expedited reporting

Sponsor should submit an IND safety report only for those events for which the sponsor determines that there is a reasonable possibility the drug caused the event, regardless of the investigator's causality assessment



Principles of clinical safety – Expedited reporting

Timelines for reporting

- **Unexpected, fatal or life-threatening, suspected:**
 - 7 calendar days (can be by phone call or fax)
 - 15 calendar days - follow-up with written IND Safety Report
- **Other serious, unexpected, suspected adverse reactions:**
 - 15 calendar days - written IND Safety Report
- Each report must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction (**AOSE**), and include an analysis of the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.
- Follow-up reports submitted as soon as information is available
- Notification to FDA and all participating investigators



Principles of clinical safety – Expedited reporting

Additional considerations

- Sponsor should evaluate all available information and decide if there is a reasonable possibility that the drug caused the adverse event
- Serious adverse events that are not likely to represent suspected adverse reactions or that are study endpoints should generally not be submitted to FDA as IND safety reports
- Sponsor should also report in an expedited manner new safety information from other sources than investigator like animal or in-vitro studies, clinical or epidemiological investigations, reports from scientific literature and scientific meetings, foreign spontaneous reports, reports from marketing experience, etc.



Principles of clinical safety – Expedited reporting

EU – Directive (2001/20/EC) and CT-3 2011

Format and means

- CIOMS I (ICH E2M = standards for transmission)
- Electronically via Eudravigilance (EVCTM) and to the NCA of the relevant member state(s) (in future the reporting to the national competent authorities will occur only via EVCTM)
- Ethic Committes should be informed within the same timeframes than CAs (but usually EC only require domestic SUSARs)



Principles of clinical safety – Expedited reporting

What needs to be reported ? Transitional arrangements

SUSARs: Suspected Unexpected Serious Adverse Reactions related to the IMP

- All SUSARs occurring in a trial irrespective of whether the SUSAR occurred at a site in a member state or a 3rd country



Principles of clinical safety – Expedited reporting

- All SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country or exclusively in another Member State, if that clinical trial, is
 - sponsored by the same sponsor, or
 - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor



Principles of clinical safety – Expedited reporting

Timelines for reporting

- Fatal & life threatening SUSARs: 7 calendar days after sponsor's awareness (any FUP within 8 further calendar days)
- All other SUSARs: not later than 15 calendar days after sponsor's awareness

Events associated with placebo usually do not satisfy the criteria for a SUSAR



Principles of clinical safety – Expedited reporting

Other Safety Issues requiring actions from sponsor

Issues which might alter the B/R assessment of the trial but which do not meet the definition of a SUSAR like:

- A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial
- A significant hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease



Principles of clinical safety – Expedited reporting

- A major safety finding from a newly completed animal study (such as carcinogenicity)
- A temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor
- Recommendations of the DSMB, if any, where relevant for the safety of the subject



Principles of clinical safety – collection, evaluation and reporting

EU vs FDA – main differences



- Most conservative approach in case of divergent opinions from investigator and sponsor
- Clock start date for reporting starts as of sponsor's awareness of a SUSAR



- Sponsor's causality assessment prevails
- Clock start date for reporting starts as of sponsor's assessment that a case requires expedited reporting



Principles of clinical safety – collection, evaluation and reporting

Challenges with unblinding

- CA and EC must receive unblinded information
- Investigators and all clinical staff must remain blinded throughout the entire study
- In some countries (USA) the investigators are the ones who inform the EC. Depending on the system used, it's not always easy to maintain the blind
- Some safety databases do not allow the generation of blinded and unblinded reports
- Rules for unblinding must be very strict and access to unblinded information on company shared repositories access limited and controlled