Safety monitoring and reporting for clinical trials in Europe

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Overview of Safety work

- **Data from preclinical studies**
  - what is expected and tolerable?
- **During administration to volunteers or patients**
  - safety measures in study protocol
  - report whatever is reported or observed
  - serious- non-serious
  - serious and expected or serious and unexpected?
- **Reference Safety Information**
  - Product specific
  - Investigator Brochure or SPC

Obligations to report

During Clinical Studies

- Serious Unexpected Serious Adverse Reactions (SUSARs)
- Annual SafetyReport (ASR)
  - New format: Development Safety Update Reports (DSUR

For Marketed Prodcts

- Periodic Safety Update Reports (PSUR)

Study protocol work

To be considered:

- Protocol structure according to ICH E6 section 6
- Safety measures in protocol (ICH E6 section 6.8)
- Special safety considerations (product related)
- Need for data monitoring board
- Safety reporting time after treatment termination

To be reported

All Adverse Reactions including

- **Severity** (mild, moderate, severe)
- **Seriousness** (serious, non-serious)
- **Relatedness** (unrelated, possibly related, probably related)

Definition of Adverse Reaction

"Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research."

Definition of Seriousness

Serious if

- results in death
- is life threatening
- requires hospitalisation, or prolongs hospitalisation
- results in persistent or significant disability or defect
- is a congenital anomaly or birth defect

Otherwise non-serious

Severity

– Is a different assessment vs. seriousness and relates to intensity of an adverse event

Causality / Relatedness

– to be reported by investigator

Sponsor is responsible to ensure that only SARs with "reasonable causal relationship" are assessed for expectedness and considered for SUSAR reporting

Definition of suspected unexpected vs. expected SARs

Definitions:

- Expected if included in Reference Safety Information, i.e. previously reported

- Unexpected unless included in Reference Safety Information

Blinded Serious Adverse Reactions

- Consider importance and consequence of unblinding
- Unblinding strongly recomended for SUSARs
- Reference is made to ICH E2A section III D

Reporting obligations during study

SAR (including SUSAR) reports

- **Investigator** to sponsor
  - immediate report within 48 hours
  - follow-up information with details

- **Sponsor** to decide if unexpected (SAR or SUSAR)

- **Sponsor** to report SUSARs to EudraVigilance Clinical Trial Module
  - within 7 days
  - follow-up information with details within an additional 8 days

Reporting obligations during study (cont'd)

Non-serious adverse events and/or laboratory abnormalities

–only if identified as critical safety information in study protocol

–to be reported by investigator to sponsor

After study termination

- **Study Report to NCA within 12 months**
  - Study report summary including main efficacy and safety results is sufficient
  - Within 6 months if paeditric population

During development (if any study ongoing)

Annual Safety Report

- An annual summary of all serious adverse events for an active compound in clinical evaluation with a safety evaluation relating to the ongoing study (ies)
- New upcoming format: DSUR

Update Investigator's brochure (IB)

- At least once per year according to Good Clinical Practice
- Include any relevant new (including safety related) data on IMP

Eudravigilance database

Set up for pharmacovigilance activities in the pre- and post- authorisation phase with two reporting modules:

–The EudraVigilance Clinical Trial Module (EVCTM) for electronic reporting of (SUSARs) as required by Directive 2001/20/EC

–The EudraVigilance Post-Authorisation Module (EVPM) designed for post-authorisation Individual Case Summary Reports

In preparation of training and reporting:

http://eudravigilance.emea.europa.eu/human/TenSteps.asp

http://eudravigilance.emea.europa.eu/human/training.asp

How to report to Eudravigilance CTM

Sponsor has overall responsibility for reporting, including time frame

–in house reporting preferred

–can delegate to Contract Research Organisation

Conclusions

Sponsor has ultimate responsibility for patient safety in clinical studies

CAs focus on patient safety in clinical trial assessment

–Secure regulatory competence for development plans

–Familiarise with safety monitoring and reporting demands