Incident management in Phase I trials: what to do if things go wrong?

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ICH E6(R2) 2.2
Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated AND CONTINUED only if the anticipated benefits justify the risks.
Q4: Do you feel adequately informed about the non-clinical data of the IMP you are working with in early clinical trials?

Answered: 63   Skipped: 14

Ensure comprehensive information on non-clinical data
Communication channels

Agree on procedures for secure and efficient communication
Stakeholder Clinical Trials
Flow of information within the Study Team

Factors that influence the flow of information

• Qualification (Study Nurse, Medic, other)
• Training (Study, Procedures)
• Personnel internal/external
• Facilities
• Availability
• Personality/communication
• Culture
• Official/inofficial rules
• Working atmosphere
Focussed flow within study team

day

weekend bank holiday

night
Risk of UNKNOWN KNOWNS*

*referring to Dr U Lorch’s presentation
Be prepared

- Training of staff
- Collaboration with hospital
  - Formal agreement
  - Contact person
  - Contacts (incl. nights, we...)
  - Medical discussion
- Knowledge of the product
- Stopping rules
- Experts available on demand

Management of emergency

- Severity?
  - Severe AE
  - Non-severe
- Seriousness?
  - SAE
  - Non-SAE
- Relationship to IMP?
  - At least possible
  - Doubtful
  - Excluded

Unblinding?

Any impact on study conduct?

Reporting?
Decision tree according to new draft EMA guidance

- SAE
  - No
    - Yes
    - No
    - On hold
      - Unblinding
        - Placebo
          - Restart
        - Verum
          - Stop dosing
      - Stop escalation
  - Yes
    - On hold
    - Unblinding
      - Placebo
        - Restart
      - Verum
        - Stop dosing

- Possible relationship
  - Yes
    - No
    - On hold
      - Unblinding
        - Placebo
          - Restart
        - Verum
          - Stop cohort
    - Stop dosing
  - No

- Severity
  - Severe
    - On hold
    - Unblinding
      - Placebo
        - Restart
      - Verum
        - Stop escalation
  - Moderate
    - On hold
    - Unblinding
      - Placebo
        - Restart
      - Verum
        - Stop escalation
### SAEs/SUSARs

- **AE**
  - **serious**
    - **Y**: INVESTIGATOR → Sponsor
      - Immediately – 24 h
    - **N**: SAE
  - **related**
    - **Y**: SPONSOR → CA / EC / Investigator
      - asap – not later than 7/15 days
    - **N**: SAE
  - **expected**
    - **Y**: Expedited reporting ‘CT-3’*
    - **N**: SUSAR
  - Non-expedited reporting ICH E2F (DSUR)

*Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use.*
Summary BE PREPARED

• Parties that safeguard subjects’ welfare: define responsibilities, ensure focussed flow of safety-relevant information
• Involve staff experienced and trained in the treatment of emergencies
• Be familiar with the compound and the study you are dealing with (IB, protocol, SmPC of comparator) \rightarrow seek information and advice
• Collaborate with near-by ICU
• Ensure availability of PI or qualified delegate 24h/7d
• Have experts available on demand (cardiologist, neurologist, psychiatrist, etc.)
• Have appropriate stopping rules in the protocol
Summary PROACTIVELY MANAGE

• Potential incident
  ▪ Is this an event that may harm the subject?
  ▪ What needs to be done to avoid progression?
  ▪ Who must be involved?
  ▪ To whom communicate which information?
  ▪ Discuss/decide with PI/delegate
  ▪ Document status and decisions

• Severe vs serious; serious? → reporting

• Apply stopping rules

• Consider involving professionals for external communication

• “lessons learned”
Usefool tools

Common Terminology Criteria for Adverse Events (CTCAE)
Version 4.0
Published: May 28, 2009 (<4.03: June 14, 2010)
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Erb-Zohar K & Donazzolo Y
Supporting questions for cases

- Is the case medically properly handled?
- Is it an SAE? If yes → reporting
- Any additional information needed?
- If it is an SAE is a possible relationship to the IMP suspected? → SUSAR?
- Is unblinding necessary?
- What are the consequences for
  - the next volunteers of the running cohort?
  - the next cohort?
  - the entire trial?
Case

Atrial fibrillation in one young male subject (FIH study, SAD, double-blind, 6+2-design)
Case

Several hours after a single oral dose of a CNS-active substance hospitalization of a 28-year old male healthy subject with suspected seizure (FIH study, SAD, double-blind, 6+2-design)
Case

After 4\textsuperscript{th} multiple dose of a cardiovascular drug malaise, palpitation, slight increase in S/DBP, mild tachycardia (multiple dose study, 2 healthy male subjects, 20-30 years old); symptoms increasing during the day, symptoms mild in 1 subject, moderate to severe in the other