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

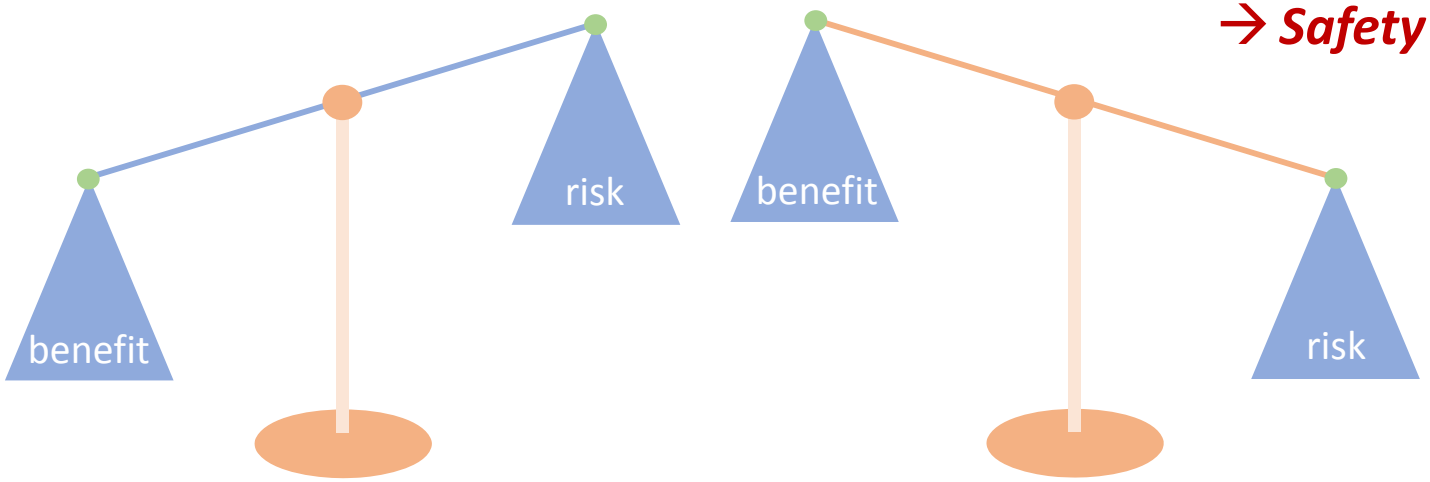
**EUFEMED Workshop 19 May 2017**

Dr Katharina Erb-Zohar, clinphase®
Planstrasse 8, 63454 Hanau, Germany
www.clinphase.com

Dr Yves Donazzolo eurofins | OPTIMED
1, rue des Essarts, 38610 Gieres, France
www.eurofinsoptimed.com

# Benefit versus Risk

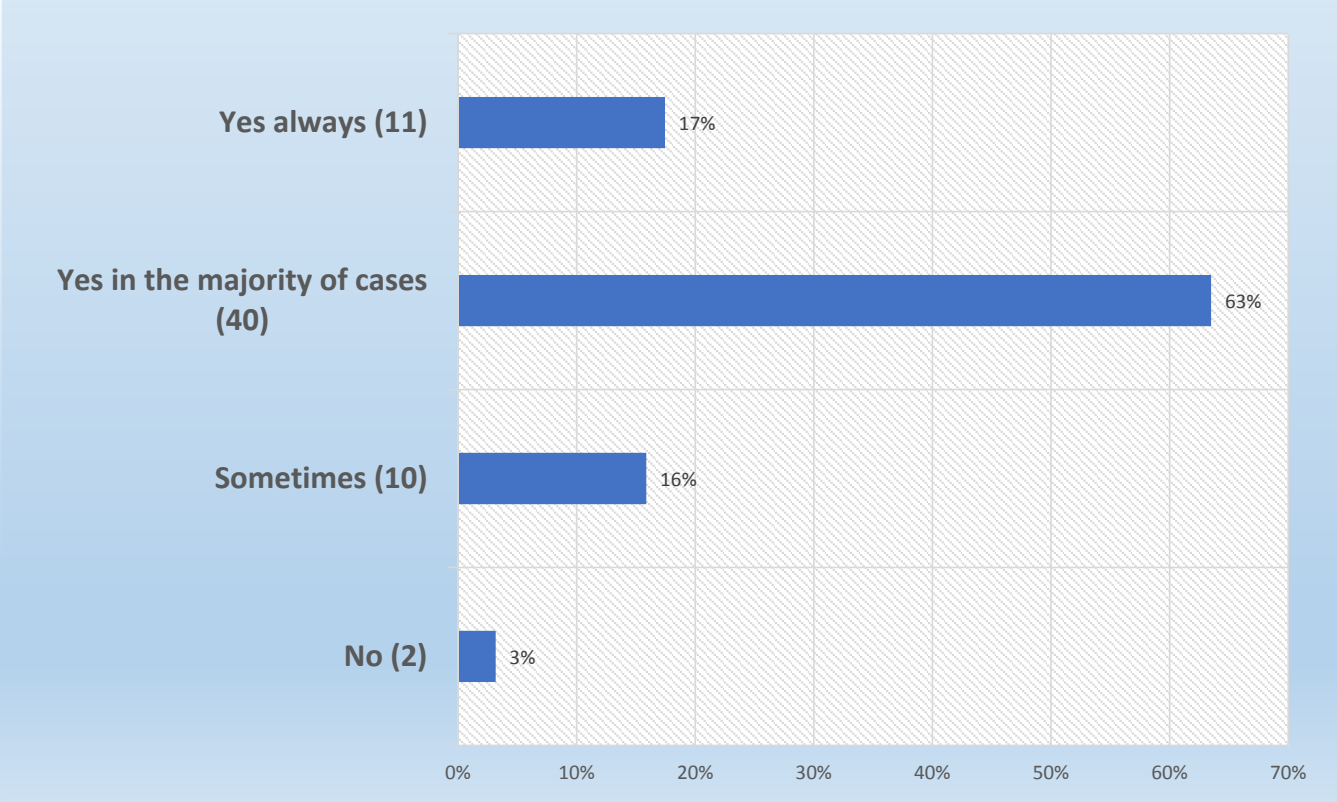
→ ***Expect the unexpected***
→ ***Safety first***




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.

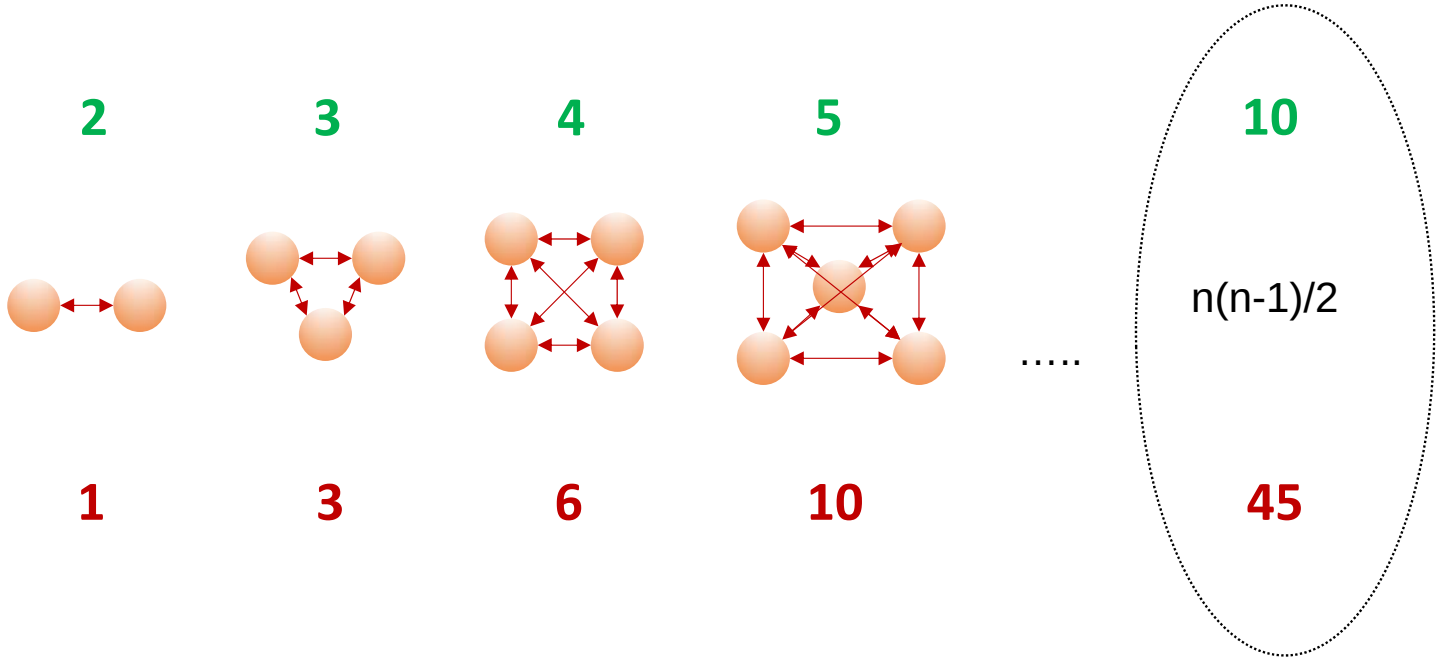
# Q4: Do you feel adequately informed about the non-clinical data of the IMP you are working with in early clinical trials?

Answered: 63 Skipped: 14



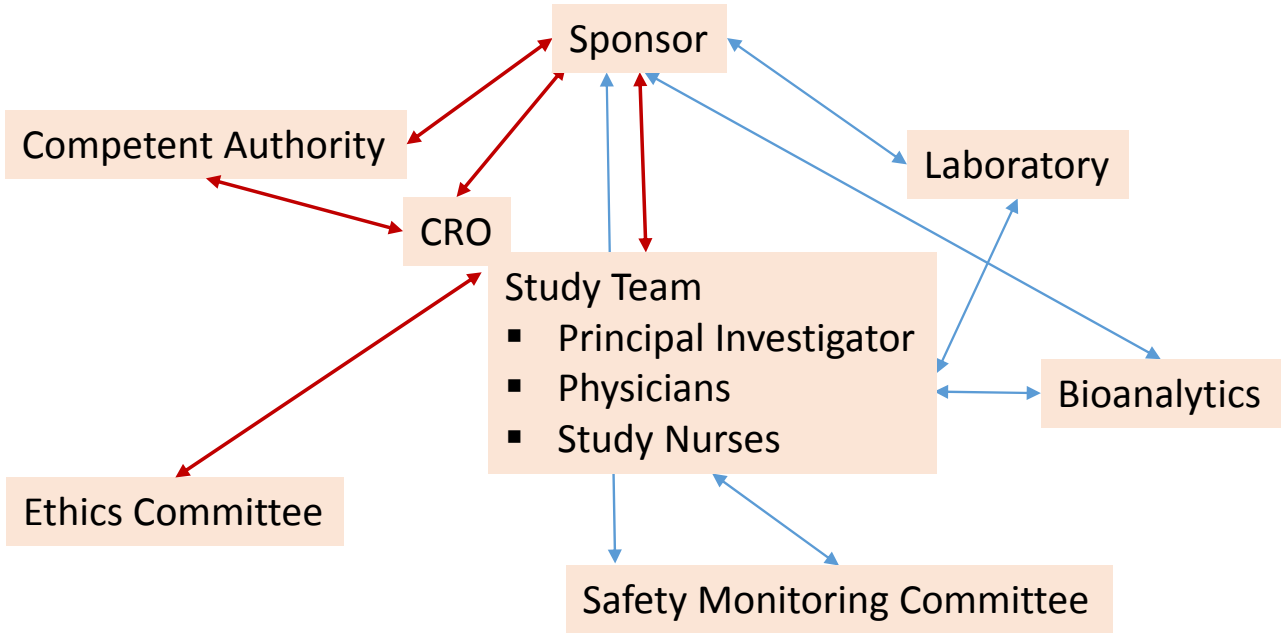

***→ Ensure comprehensive information on non-clinical data***

## Communication channels

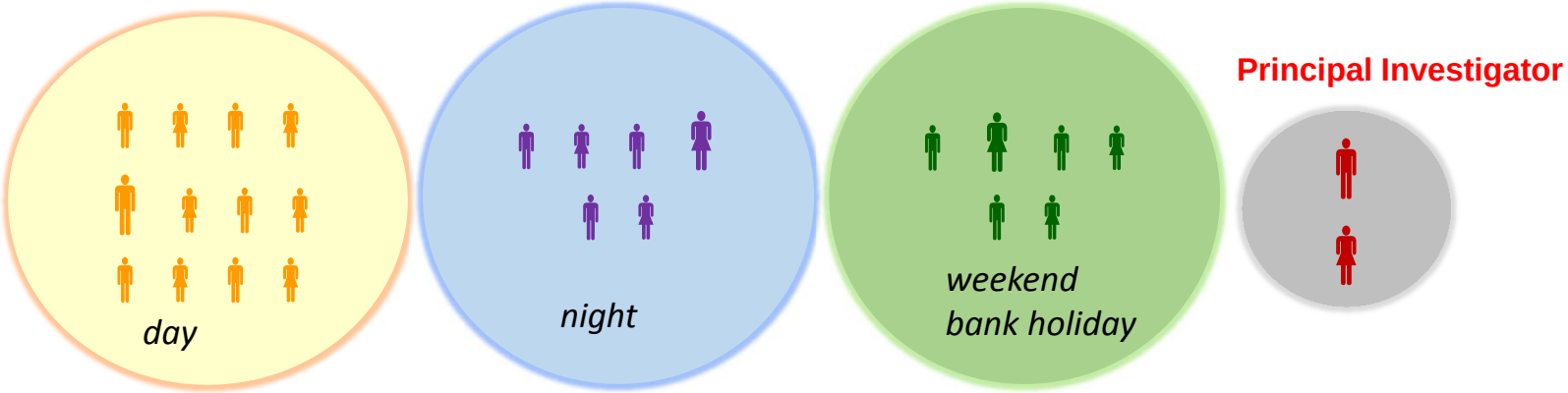



→ ***Agree on procedures for secure and efficient communication***

# Stakeholder Clinical Trials



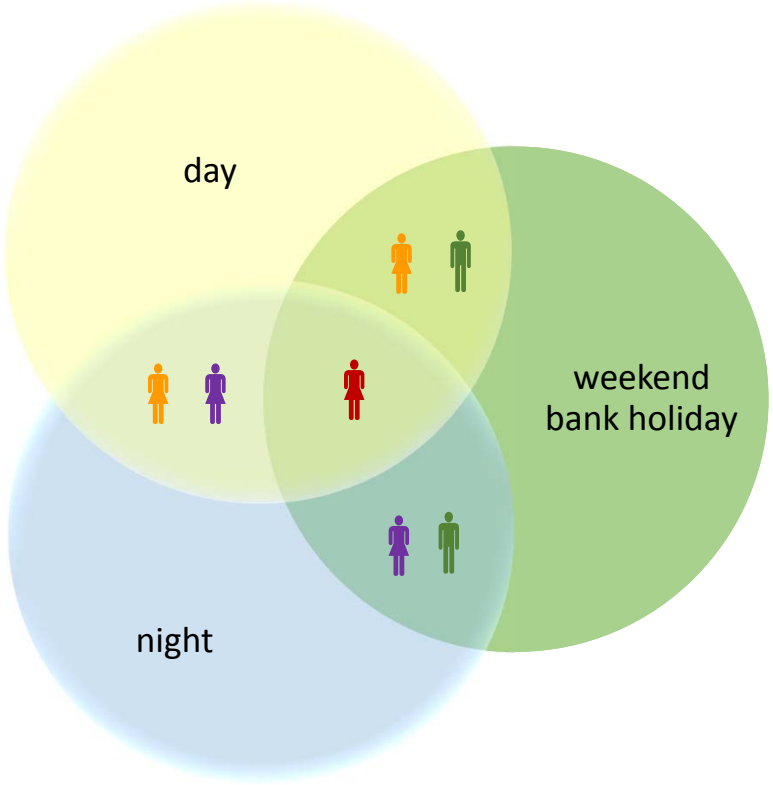
# Flow of information within the Study Team




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



**Expertise / Experience**
**Training**
**Communication**

**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

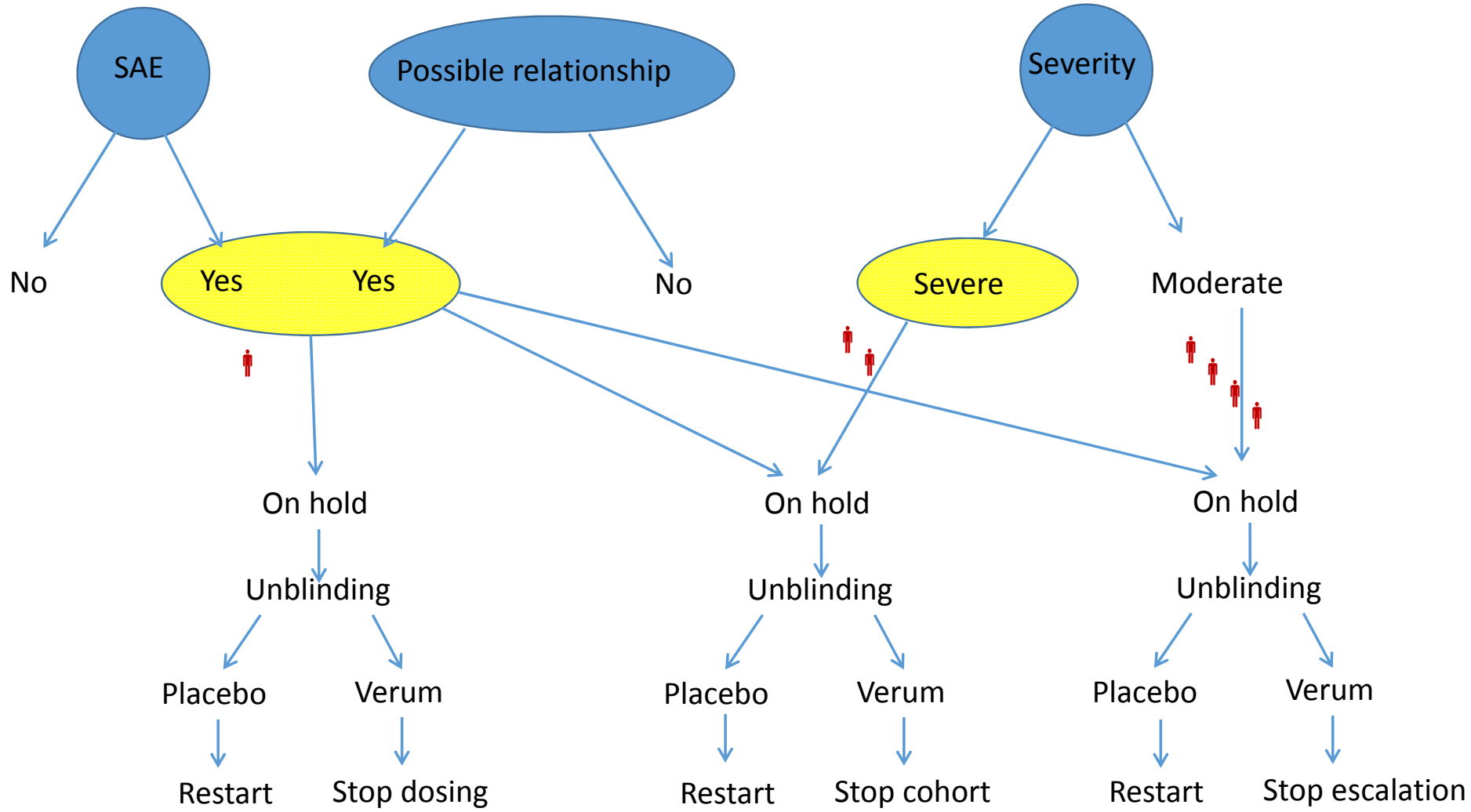
- Severity ?
  - Severe AE
  - Non-severe
- Seriousness ?
  - SAE
  - Non-SAE
- Relationship to IMP ?
  - At least possible
  - Doubtful
  - Excluded

**Unblinding ?**

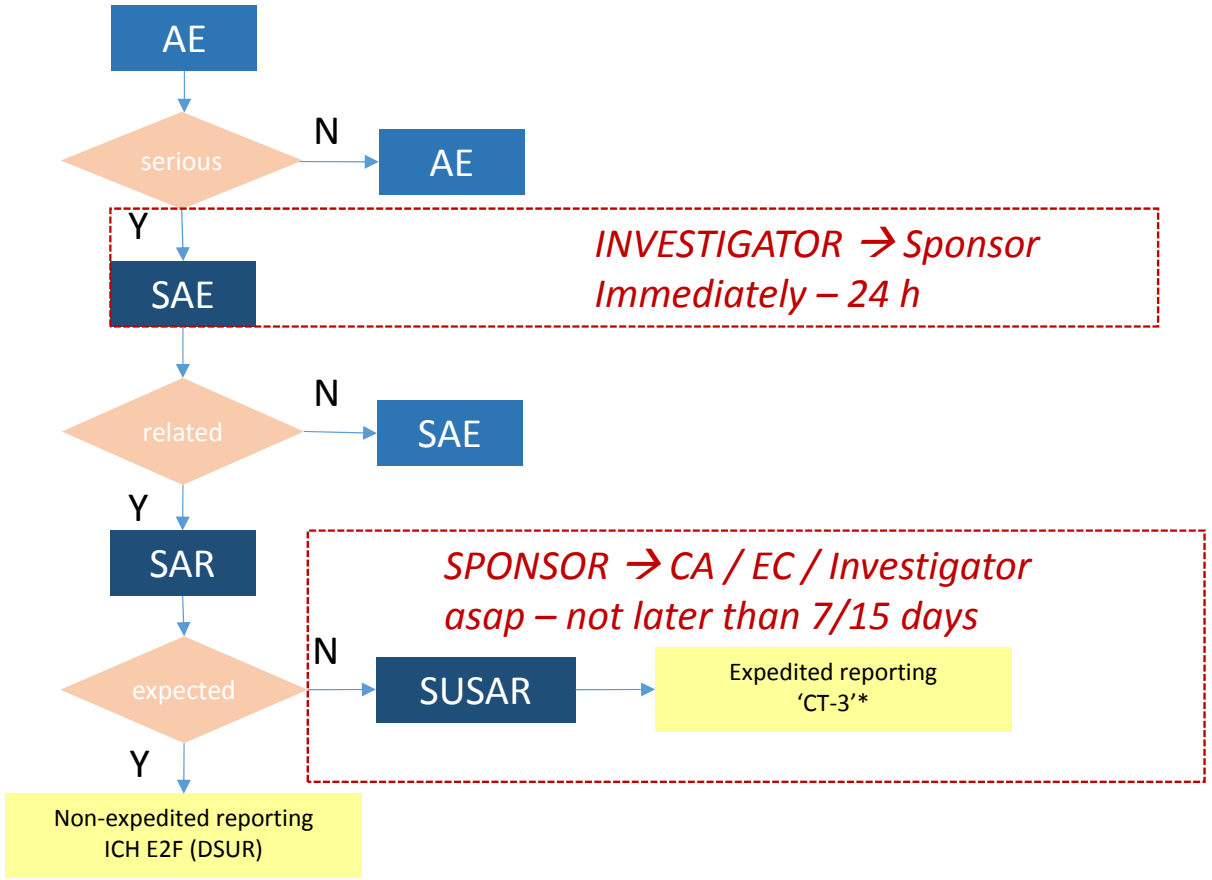
**Any impact on study conduct ?**

**Reporting ?**

## Decision tree according to new draft EMA guidance



# SAEs/SUSARs




*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) → 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“

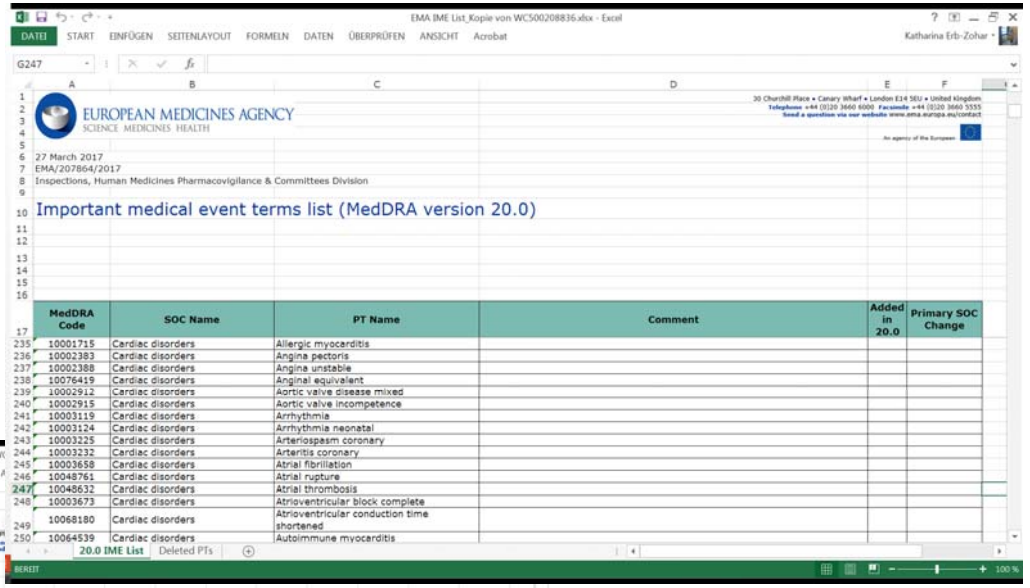
# Usefool tools

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2017
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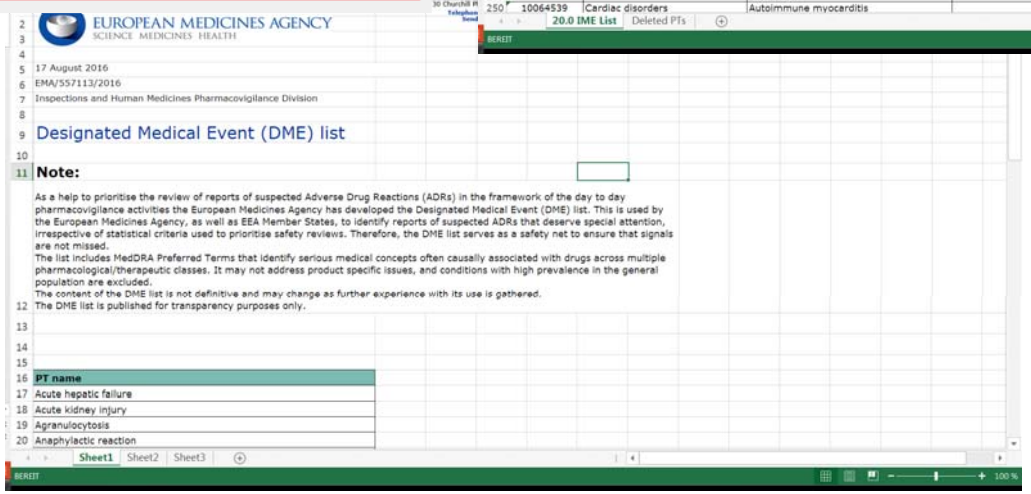
Inspections, Human Medicines Pharmacovigilance & Committees Division

Important medical event terms list (MedDRA version 20.0)

| MedDRA Code | SOC Name | PT Name | Comment | Added in 20.0 | Primary SOC Change |
|---|---|---|---|---|---|
| 10001715 | Cardiac disorders | Allergic myocarditis | | | |
| 10002383 | Cardiac disorders | Angina pectoris | | | |
| 10002388 | Cardiac disorders | Angina unstable | | | |
| 10076419 | Cardiac disorders | Anginal equivalent | | | |
| 10002912 | Cardiac disorders | Aortic valve disease mixed | | | |
| 10002915 | Cardiac disorders | Aortic valve incompetence | | | |
| 10003119 | Cardiac disorders | Arrhythmia | | | |
| 10003124 | Cardiac disorders | Arrhythmia neonatal | | | |
| 10003225 | Cardiac disorders | Arteriospasm coronary | | | |
| 10003232 | Cardiac disorders | Arteritis coronary | | | |
| 10003658 | Cardiac disorders | Atrial fibrillation | | | |
| 10048761 | Cardiac disorders | Atrial rupture | | | |
| 10048632 | Cardiac disorders | Atrial thrombosis | | | |
| 10003673 | Cardiac disorders | Atrioventricular block complete | | | |
| 10068180 | Cardiac disorders | Atrioventricular conduction time shortened | | | |
| 10064539 | Cardiac disorders | Autoimmune myocarditis | | | |



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 August 2016
EMA/557113/2016
Inspections and Human Medicines Pharmacovigilance Division

Designated Medical Event (DME) list

**Note:**

As a help to prioritise the review of reports of suspected Adverse Drug Reactions (ADRs) in the framework of the day to day pharmacovigilance activities the European Medicines Agency has developed the Designated Medical Event (DME) list. This is used by the European Medicines Agency, as well as EEA Member States, to identify reports of suspected ADRs that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews. Therefore, the DME list serves as a safety net to ensure that signals are not missed.
The list includes MedDRA Preferred Terms that identify serious medical concepts often causally associated with drugs across multiple pharmacological/therapeutic classes. It may not address product specific issues, and conditions with high prevalence in the general population are excluded.
The content of the DME list is not definitive and may change as further experience with its use is gathered.
The DME list is published for transparency purposes only.

| PT name |
|---|
| Acute hepatic failure |
| Acute kidney injury |
| Agranulocytosis |
| Anaphylactic reaction |

# 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 4th 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