



# Stopping rules for FIM trials

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# Relevant Guidelines

EMA/ CHMP/ SWP/ 294648/ 2007

“Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products”

## Introduction

- „The safety of subjects participating in first in human studies is the paramount consideration as they would not normally be expected to derive any therapeutic benefit.“

## Clinical aspects

- „The protocol should describe the strategy for managing risk including a specific plan to monitor for and manage likely adverse events or adverse reactions as well as the procedures and responsibilities for modifying or stopping the trial if necessary.”
- “The protocol should define stopping rules for the cohort and trial. It should define processes and responsibilities for making decisions about dosing of subjects, dose escalation and stopping the cohort or trial.“

# Tolerability as an objective for FIM trials?

One (of many others) or the most important objective?

- Results from healthy subjects partly not predictive for patients
- DoTS (dose-time-susceptibility) classification of adverse events (Aronson, Ferner 2003)
  - direct toxic effects (high doses / concentrations)
  - collateral effects (therapeutic doses / concentrations)
  - hypersusceptibility reactions (at low concentrations in susceptible subjects)
  - → often not predictable
- Low probability to detect rare AEs within the usual cohort size  
e.g. AE with an incidence of 0.1 → probability to detect it with  $n=20 = 0.02$

# MTD as target for dose escalation in FIM?

MTD=Maximum tolerated dose

- Defined and characterized especially with regard to investigating toxicity (e.g. ICH-M3)
- Mentioned in the FDA guidance:  
„In a toxicity study, the highest dose that does not produce unacceptable toxicity“ (FDA guidance for Industry, CDER, 2005, “Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers“)
- Not mentioned in the EMA guideline EMA/CHMP/SWP/ 294648, 2007 („Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products“)

# MTD as target for dose escalation in FIM?

- Searching for “Maximum tolerated dose” in Google
  - 1.7 Mio hits
  - 2.8 Mio hits when combined with “Clinical trials”
  - 3.9 Mio hits when combined with “First in man trial”
- Search in Pubmed  
„Maximum tolerated dose“ and „First in man trial“  
33 hits, mostly for cancer trials
- Clinicaltrials.gov:  
„Maximum tolerated dose“ and „First in man trial“  
21 trials, mostly cancer, 2 for healthy subjects in other indications
- EU Clinical trials register:  
„Maximum tolerated dose“ and „First in man trial“  
1 trial (cancer)

# MTD as target for dose escalation in FIM?

- Described as goal of dose escalation in e.g. publications, but no further specification of „maximum tolerability“ is given
- Justified with „therapeutic dose range has to be exceeded by significant factor“ but therapeutic dose range not yet known
- Argumentation with suprathreshold doses which are needed for subsequent TQT- and DDI- trials but not all drug candidates reach this step of clinical development

## Adverse events healthy subjects– data from literature

- Tolerability data for healthy subjects in FIM trials difficult to find in literature (Wensing et al, 2010; 24 FIM trials at Bayer/ Schering, 1094 healthy male subjects)
- Some more publications regarding tolerability in (early) clinical pharmacology trials with healthy subjects
  - Lutfullin et al, 2005; 142 studies with 1559 participants, 32 different drugs and placebo at Bayer
  - Sibille et al, 1997; all AEs in a Phase I centre during 10 years, 1015 healthy volunteers
  - Ighrayeb et al (poster presentation), Bayer, 86 early Phase I trials, 1996 healthy subjects

## Could one consider Phase I as safe?

- Sibille et al, Br J Clin Pharm 2006

- In the literature 15 deaths have been published during the last 30 years in the Western Countries, although ca. 100.000 subjects were dosed every year
- SAE register of Club Phase I, only for healthy subjects in Phase I trials, data for 2004-2005 from 15.386 healthy subjects
- 2 deaths (not related to study drug)
- 60 other SAEs, 8 of them were worrying with high risk,
  - 3 out of 8 related to study drug – rash and fever
  - agranulocytosis
  - long lasting atrial fibrillation
- SAE – incidence – 0,4%, but higher in elderlies (2%)
- Japanese register 1993 – 2004, 95.780 subjects, no deaths, low incidence of SAEs (0.05%)

➔ **The risk of SAE in Phase I is low when common safety rules are applied.**

# Grading of adverse events and other safety findings

- Grading is directly derived from „observed intensity/severity“, the „daily life consequences“ and the need for concomitant medication
  - Generally applicable for discontinuous variables like e.g. AEs
  - Grade 1 – does not interfere with daily activity
  - Grade 2 - interferes with daily activity, no treatment required (except e.g. paracetamol)
  - Grade 3 – prevents daily activity or requires treatment
  - Grade 4 – life threatening, exceptional in Phase I studies, supports a stopping decision

(Sibille et al, BJCP, 2010)

# Stopping rules

- At the individual (subject) level
  - General rule based on risk assessment, i.e. stop dose escalation if any event equal or superior a certain level (usually 3) occurs
  - All other available information should be taken into consideration (i.e. time relative to drug administration, association with other safety signals)
  - Upgrading in case of
    - any association of a finding to a clinical symptom(s) or sign(s),
    - or a rapid worsening,
    - or a concomitant modification of any other relevant parameter(s) (e.g. ALT and bilirubin, CPK and AST, creatinine and hyperkalaemia)

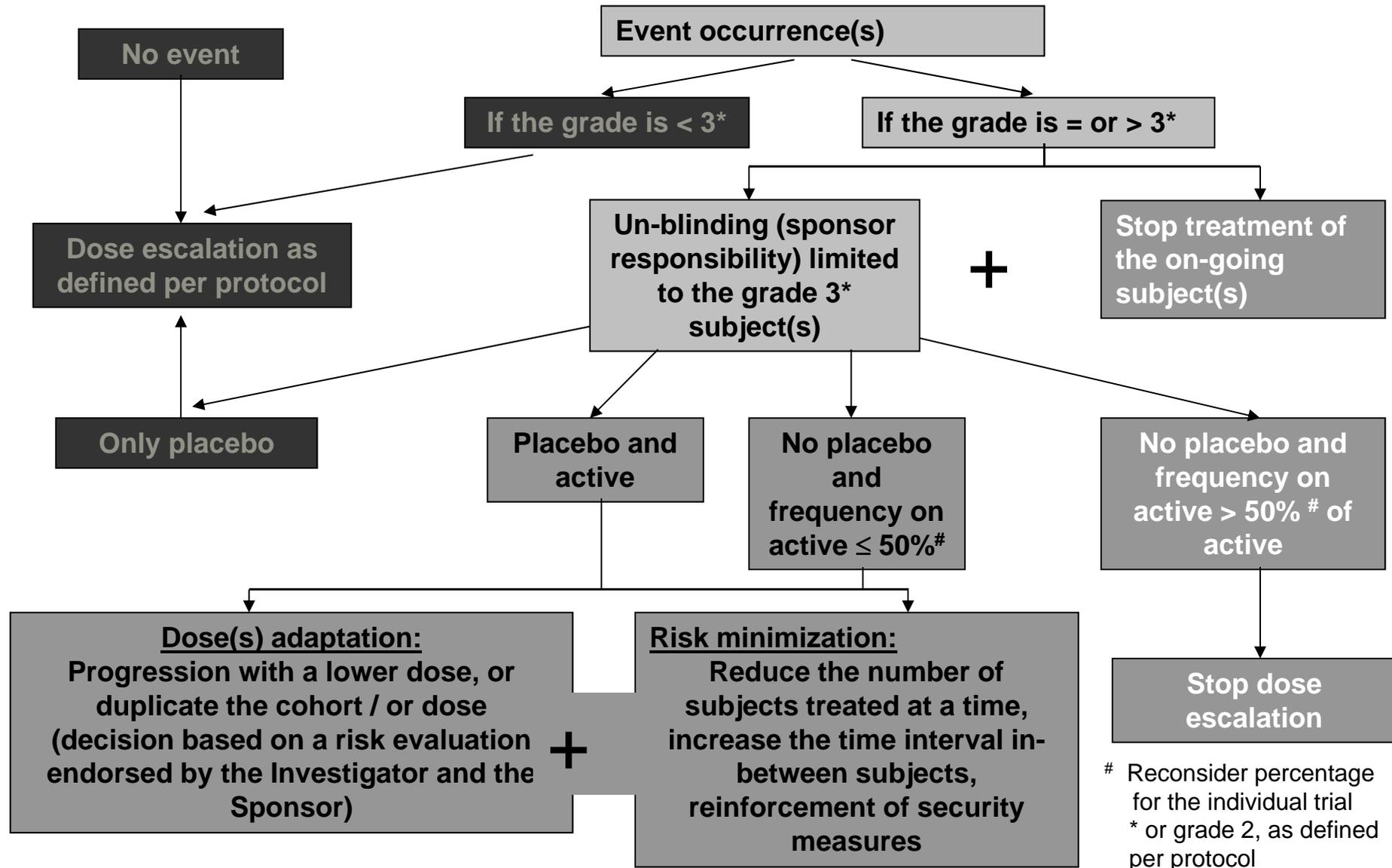
(Sibille et al, BJCP, 2010)

# Stopping rules

- At the cohort level
  - More complex process than for a single subject is required
  - To be considered:
    - type of the event and its intensity
    - its monitorability
    - its reversibility and possible outcome (complications)
    - the number of subjects experiencing this adverse event
    - type of administered drug (placebo, verum)
  - Proposed algorithm is based on the small number of subjects, the rarity of the events, the possible high risk potential (consider unblinding of single subjects in case of risky events)

(Sibille et al, BJCP, 2010)

# Algorithm for decision making for dose escalation at the cohort level (Sibille et al, BJCP, 2010)



# Reconsider percentage for the individual trial  
\* or grade 2, as defined per protocol

# Risk-benefit related stopping criteria for a FIM trial (example)

## ○ **Subject level:**

- A serious adverse event related to the trial medication
- Subject's partner becomes pregnant
- Any relevant deterioration in the health of the subject (AEs, vital signs, ECG, laboratory parameters)
- Clinically relevant QT or QTcB interval prolongation
- Clinically relevant change in liver or renal parameters
- Clinically relevant change in vital signs if technical failure can be excluded and result is confirmed by at least 1 additional measurement

## ○ **Stopping of the dose escalation:**

- More than 50% of all subjects who received IMP at the previous dose step experienced the same severe treatment emergent adverse event with at least possible relationship to IMP as assessed by the RBC.
- At least 1 subject who received IMP in the previous dose step experienced a medically serious adverse event with at least possible relationship to IMP as assessed by the RBC.

**Thank you for your attention**