When is a subject healthy?

Results of an AGAH Discussion Platform

Dr. Kerstin Breithaupt-Grögler
Frankfurt, Germany
e-Mail: breithaupt-groegler@t-online.de

Prof. Dr. Hildegard Sourgens
Munich, Germany
e-Mail: info@sourgens.de
Risk Mitigation in Clinical Trials via General Code of Conduct

Risk assessment regarding a new compound is primarily performed by the **Sponsor** (ICH-GCP)

Approval of **Competent Authorities** and **Ethics Committees** protects subject’s safety, assures scientific soundness of protocol, and trial conduct according to local law and regulatory guidance (ICH-GCP)

The **Investigator** is responsible for the clinical well-being of the trial subject; this responsibility is not waived by informed consent; well-being of trial subject prevails over all other interests (Declaration of Helsinki)
Healthy subjects’ trial warrants very low tolerance for risk
When is a subject healthy?

- „A healthy person is a person who has not been thoroughly examined“
- Sociocultural aspects define who is regarded as fit and healthy
- Is a trial subject representative for a healthy person in the respective country / sociocultural context?
AGAH Platform for Debate – Part I

AGAH WORKSHOP

DISKUSSIONSFORUM:

WANN IST DER
GESUNDE PROBAND
„GESUND GENUG“
FÜR DIE
KLINISCHE PRÜFUNG?

12. NOVEMBER 2012, BONN

REFERENTEN / VORSITZENDE / ROUND-TABLE TEILNEHMER

Dr. med. Kerstin Breithaupt-Gröger
  kbr- clinical pharmacology services, Frankfurt am Main

Dr. med. Frank Donath
  Socratec GmbH, Erfurt

Dr. med. Klaus Francke
  Parexel GmbH, Berlin

Dr. med. Mario Iovino
  Boehringer Ingelheim GmbH & Co KG, Biberach a. d. Riss

Reinhard Schinzel
  vasopharm GmbH, Würzburg

Prof. Dr. med. Hildegard Sourgen
  Consultant, München

PD Dr. med. Thomas Sudhop
  Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn

Dr. med. Wolfgang Timmer
  CRS Clinical Research, Mannheim

Prof. Dr. med. Georg Weusing
  Bayer Health Care, Wuppertal
AGAH Platform for Debate – Part II

AGAH WORKSHOP

FORTSETZUNG DES DISKUSSIONSFORUMS

WANN IST DER GESUNDE PROBAND „GESUND GENUG“ FÜR DIE KLINISCHE PRÜFUNG?

26. SEPTEMBER 2013, BONN

REFERENTEN / VORSITZENDE / ROUND-TABLE TEILNEHMER

Dr. Kerstin Breithaupt-Grögler
-ker- clinical pharmacology services, Frankfurt am Main
Margareta Bost
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Dr. Frank Dunath
Socrates GmbH, Erfurt
Dr. K. Erb-Zohar
clinphase, Hanau
Dr. Georg Geler
Parexel GmbH, Berlin
Dr. Karin Göhler
Grunenthal GmbH, Aachen
Dr. Susanna Hausmann
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Dr. Mario Iovino
Boehringer Ingelheim GmbH & Co KG, Biberach a. d. Riss
Dr. Kerstin von Mallinckrodt
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Dr. Aylin Menke
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Prof. Dr. Gerd Mikus
Abt. Klinische Pharmakologie, Universität Heidelberg
Heiko Preißler
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Dr. Jens Rengelshausen
Grunenthal GmbH, Aachen
Prof. Dr. Hildegard Sorge
Consultant, München
Dr. Elke Stahl
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Barbara Stommel
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
PD Dr. Thomas Studhop
Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn
Dr. Wolfgang Timmer
InaMed GmbH, München
Major Issues of Debate

- Screening examination
  - Timing prior to first dose
  - Screening results vs. baseline findings

- Safety parameter
  - Timing throughout the trial
  - Exclusion criteria: What is 'normal' regarding vital signs, ECG, safety laboratory parameters?
  - General assessments – how to minimise risk

- Stopping criteria*
  - Risk adapted approach
  - Individual subject
  - Dose group / stop of further dose escalation
  - Termination of entire trial

* Preliminary conclusions of debate
Screening Examination - Timing

- First-in-man trial
  - Check laboratory values and inclusion / exclusion criteria between 48 to 72 h prior to first dosing (3 calendar days)
  - If screening performed more than 72 h prior to first dosing, repeat laboratory assessments and check whether relevant changes / important events occurred; medical examination by trial physician to confirm subject eligibility; these examinations are regarded as part of screening

- Well known and generally safe medicines (e.g. bioequivalence trial)
  - Screening examination usually between -21 to-1 days prior to first dosing; take risk-adapted approach
Screening Examination

- All clinical trials with healthy subjects
  - The decision whether inclusion / exclusion criteria are met / not met is taken at the timepoint of the screening examination
  - Baseline assessments (e.g. immediately prior to first dosing) are not performed to reassess inclusion/exclusion criteria but to define the baseline values for all subsequent measurements
  - Safety-relevant stopping criteria that were defined in the protocol also apply to baseline findings
  - If time period between screening examination and dosing was considerably long, a risk-adapted (re)examination by the trial physician is recommended prior to dosing
Major Issues of Debate

- **Screening examination**
  - Timing prior to first dose
  - Screening results vs. baseline findings

- **Safety parameter**
  - Timing throughout the trial
  - Exclusion criteria: *What is „normal“ regarding vital signs, ECG, safety laboratory parameters?*
  - General assessments – how to minimize risk

- **Stopping criteria***
  - Risk adapted approach
  - Individual subject
  - Dose group / stop of further dose escalation
  - Termination of entire trial

*Preliminary conclusions of debate*
Safety Parameter - Timing

- In all trials, a baseline assessment prior to first dosing and an end-of-trial examination after last dosing (e.g. laboratory values and vital signs) are performed to document relevant findings at start and end of the trial.

- This is recommended for scientific as well as for legal reasons.

- Time points of additional assessments are to be defined in the protocol according to scope and duration of the trial.
Heart rate – Normal ranges

First-in-man trial

- Range between 50 and 90 bpm is recommended

- Some participants of panel discussion find also heart rate <50 and ≥45 bpm acceptable in case of normal thyroid function (medical history, physical examination, TSH) and no signs of diseases associated with bradycardia plus eventually normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach
Well known / generally safe medicines (e.g. bioequivalence trial)

- Range between 50 and 90 bpm is recommended
- Eventually heart rate <50 and ≥45 bpm acceptable in case of normal thyroid function (medical history, physical examination, TSH) and no signs of diseases associated with bradycardia
- Some participants of panel discussion find also heart rate <45 bpm acceptable in case of above stated criteria plus normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach
Heart Rate – Normal Ranges

How to measure heart rate?

✔ Preferably count full 60 sec via palpation of peripheral pulse or use ECG strip over 60 sec

✔ If results from automatic outputs from shorter assessments (e.g. 25 sec ECG strip or automatic blood pressure measurements) indicate values outside of the reference ranges, full counts to be performed to validate assessments
Laboratory Parameters – Normal Ranges

- First-in-man trial
  
  - Relevant hepatic (ALT/GPT, AST/GOT, bilirubin*, eventually also AP and GGT) and renal parameter (creatinine, estimated GFR according to Cockcroft-Gault or alternative formulae) not to exceed ULN
    
    * elevated bilirubin in case of Gilbert’s disease is not clinically relevant, may however hamper interpretation of eventual drug effects
  
  - Amylase and Lipase to be interpreted in a clinical context
  
  - Protocol to present a rationale whether additional laboratory parameters are required not to exceed reference ranges
Well known / generally safe medicines (e.g. bioequivalence trial)

- Slightly elevated hepatic (10% above ULN for ALT/GPT bis, 20% above ULN for AST/GOT or bilirubin*) or renal parameters (up to 0.1 mg/dL increase in creatinine) acceptable if no indication of apparent disease
- * in case of Gilbert’s disease also higher bilirubin levels are observed without being of clinical relevance; this may however hamper interpretation of eventual drug effects

- Protocol to present a rationale why these abnormal laboratory parameters seem acceptable

- GFR und creatinine clearance may be estimated via appropriate formulae
All trials with healthy subjects

- In general, exclusion criteria applied for screening examinations are appropriate
- QTcF to be normal
- 1st degree AV-Block seems acceptable in case heart rate within reference ranges and no signs of cardiac dysfunction / disease
Blood Pressure – Normal Ranges

- All trials with healthy subjects
  - ✓ In general, current exclusion criteria applied for screening examinations are appropriate
  - ✓ Normal ranges to be defined in protocol
Risk mitigation via definition of normal ranges

- Definition of normal ranges intends to **minimise risk** and to increase subjects’ safety
- Are subjects with abnormal values **representative for the healthy population**?
- Definition of normal ranges intends to **increase noise-effect ratio** regarding eventual drug actions
- **Out-of-range screening/baseline values** potentially obstruct the detection of drug effects
Risk mitigation via definition of normal ranges

- But: also drug-induced changes within the reference ranges may be relevant
- But: also trial conditions (e.g. no caffeine, no smoking, no sports) may affect safety parameter
- But: tick-box approach screening cannot replace thorough and complex medical decisions taken by the investigator
**Major Issues of Debate**

- **Screening examination**
  - Timing prior to first dose
  - Screening results vs. baseline findings

- **Safety parameter**
  - Timing throughout the trial
  - Exclusion criteria: What is „normal“ regarding vital signs, ECG, safety laboratory parameters?
  - General assessments – how to minimize risk

- **Stopping criteria***
  - Risk adapted approach for FIM
  - Individual subject
  - Dose group / stop of further dose escalation
  - Termination of entire trial

* Preliminary conclusions of debate
Stopping Criteria for FIM

- Risk-adapted approach
  - Protocol to present toxicological targets indicated by non-clinical studies (based on Investigator’s Brochure)
  - Beware if there are none: wrong species, wrong model, wrong parameter, wrong ...? - consult with Competent Authority
  - Protocol to define stopping criteria and decision making process for individual subject, cohort (dose group), and entire trial
  - Algorithm published by Sibille et al. in 2010 serves as a good starting point

Stopping Criteria for FIM

For the individual subject

- Coding adverse events and laboratory abnormalities according to CTC-AE\* criteria / grades facilitates definition of stopping criteria, even though CTC-AE not really suitable for healthy subjects
- 1 adverse event of severe intensity (Grade 3)
- 1 serious adverse event
- Relevant signs and symptoms affecting subject safety
- Decision is always taken by the investigator

\* Common Terminology Criteria for grading of Adverse Events developed by National Cancer Institute (NCI) 
1=mild, 2=moderate, 3=severe, 4=life-threatening, 5=death
Stopping Criteria for FIM

- For a dose group – stop of further dose escalation
  - In case of relatedness of adverse events in individual subjects, consequences may arise regarding further dose escalation
  - \( \geq 50\% \) of subjects of the preceding dose step experienced adverse events of moderate (Grade 2, ‘safety alert, warning signal?’) or severe (Grade 3) intensity and at least possible relationship to trial medication (selective unblinding)
  - 1 serious adverse drug reaction (unblinding advised)
  - In case trial is to be continued following safety consultation between all stakeholders, a substantial amendment is required
Stopping Criteria for FIM

- Termination of entire trial
  - Decision for trial termination is taken by mutual agreement between investigator and sponsor
Stopping Criteria for later Phase I Trials

- General risk assessment based on
  - **Exposure** (e.g. high exposure in drug-drug interaction trials, thorough QT trials)
  - Frequency of relevant adverse events
- Protocol to define stopping criteria and decision making process for individual subjects, cohorts, and entire trial
Action Points

- Reference ranges for healthy subjects to be redefined taking into account age, gender, BMI, nutrition habits, general condition, physical activity
- Independent database to be set up regarding baseline conditions and placebo effects; all trial centers should contribute to this database
- Expert group advising on specific problems to be established
- Discussion platform to be continued on regular basis with 1-2 meetings per year
- Next Meeting Autumn 2014
  - Umbrella protocols – vice or virtue?
  - Pros and Cons of adaptive designs