Risk mitigation in early phase clinical trials

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nothing to disclose
Risk mitigation in early phase clinical trials

Question 1.
The pharmaceutical industry (sponsor of a clinical study) is responsible for the patients’/volunteers’ safety in the clinical study.

Yes  (green)
No  (red)

Risk mitigation in early phase clinical trials

Question 2.
The aim of a first-in-man (FIM) study is to find the therapeutic dose.

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Risk mitigation in early phase clinical trials

Question 3.
The risk for a healthy person participating in an early phase study of being hospitalized for drug related adverse events is higher than for accidents during the study period.

Yes (green)
No (red)

Risk mitigation in early phase clinical trials

1. Facts on drug development
Drug development

- >20,000 molecules → 1 medicine
- Development cost >1 billion Euro
- Development time: 12-15 years
- Phases of drug development
  - Preclinical (6 years)
    - Effect and toxicity on cells, organs, animals
  - Clinical phase (6-9 years)
### Phases of clinical drug research

<table>
<thead>
<tr>
<th>registration</th>
<th>phase</th>
<th>goal</th>
<th>volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>early phase</td>
<td>Max. Tolerable Dose (MTD)</td>
<td>Healthy or patient</td>
</tr>
<tr>
<td>pre</td>
<td>dose range effect + AE</td>
<td>patient</td>
<td>small</td>
</tr>
<tr>
<td>pre</td>
<td>late phase</td>
<td>treatment effect + AE</td>
<td>Patient</td>
</tr>
<tr>
<td>post</td>
<td>Post Marketing Surveillance (PMS)</td>
<td>patient</td>
<td>very large</td>
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</table>

### Risk mitigation in early phase clinical trials

1. Facts on drug development
2. Guidelines for clinical drug development
GCP/ICH
GCP: good clinical practice
ICH: international conference on harmonisation

AIM
• Preserve rights of healthy/patient volunteers
• Improve quality of clinical studies

In EU Directive 2001
To be implemented by EU member states 2004

Some important GCP/ICH rules
• Studies to be approved by Ethics committee (EC)
• Studies to be approved by the country’s competent authority (CA; representing EMA)
• Persons willing to participate in a study have to be informed orally and in writing
• Subjects can withdraw from study without obligation mentioning reason and without any consequence for his/her treatment
• The sponsor is owner of study data and responsible for submission of study to EC & CA
• The investigator is responsible for the safety of the subjects participating in the study
ICH-GCP
Investigator's responsibilities

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Declaration of Helsinki: avoid damage to volunteers by all means

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

Investigator is responsible for healthy subjects'/patients' safety

Risk mitigation in early phase clinical trials

1. Facts on drug development
2. Guidelines for clinical drug development
3. How to choose the first dose in man
Goals of nonclinical safety evaluation:
- characterization of toxic effects
- dose dependency
- relationship to exposure (AUC) & Cmax
- reversibility

Information is used to:
- estimate safe starting dose
- estimate dose range for human trials
- identify parameters for clinical monitoring of potential AEs

Non-clinical data needed for full development

Pharmacology studies
- Core battery of safety pharmacology studies includes effects on cardiovascular, central nervous, respiratory systems
- mode of action/effect on therapeutic target

Genotoxicity studies
- phase-I single dose: assay for gene mutation (AMES test)
- phase-I multiple dose: tests for chromosomal damage in mammals

Phase-II: complete battery of tests for genotoxicity

Carcinogenicity studies
For clinical trials only needed if significant concern of carcinogenic risk
Non-clinical data needed for full development

Repeated-dose toxicity studies in 2 mammalians, at least 1 is a non-rodent

<table>
<thead>
<tr>
<th>max duration of clinical trial</th>
<th>recommended min duration of repeated-dose toxicity studies</th>
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<tbody>
<tr>
<td></td>
<td>rodents non-rodents</td>
</tr>
<tr>
<td>≤ 2 weeks</td>
<td>2 weeks</td>
</tr>
<tr>
<td>2 weeks-6 months</td>
<td>= clinical trial = clinical trial</td>
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<tr>
<td>&gt; 6 months</td>
<td>6 months 9 months</td>
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</table>

Selection of Maximum Recommended Starting Dose for drugs administered systemically to normal volunteers

Step 1: Determine NOAELs (mg/kg) in toxicity studies

Is there reason to believe that toxic doses do not scale by body surface area?

No → Convert each animal NOAEL to Human Equivalent Dose (HED) (based on body surface area)

HED (mg/kg) = NOAEL (mg/kg) (or other appropriate normalization)

Yes → Pick HED from most appropriate species

Step 4: Choose Safety Factor and divide HED

Maximum Recommended Starting Dose (MRSD)

Step 5: Consider lowering dose based on a variety of factors, e.g., the PAD

No → Lower dose based on a variety of factors, e.g., the PAD
Step 1: No observed adverse effect level (NOAEL) determination

- **NOAEL:**
The highest dose level that does not produce a significant increase in adverse effects

- **Adverse effect:**
Statistically significant or clinically significant

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Step 1: No observed adverse effect level (NOAEL) determination

- **Three types of findings to determine NOAEL:**
  - overt toxicity (e.g., clinical signs, macro- and microscopic lesions)
  - surrogate markers of toxicity (e.g., serum liver enzyme levels)
  - exaggerated pharmacodynamic effects
Step 2: Human Equivalent Dose (HED) calculation

- Aim: to correct for species differences in metabolism/drug elimination
- Conversion based on Body Surface Area
- Conversion based on mg/kg (if in all species NOAEL occurs at same mg/kg)
- Approach based on PK: AUC (and Cmax)
### Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area

<table>
<thead>
<tr>
<th>Species</th>
<th>To convert animal dose in mg/kg to dose in mg/m², multiply by km below:</th>
<th>To convert animal dose in mg/kg to HED in mg/kg, either:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Divide animal dose by:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiply Animal dose by:</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>Child (20 kg)</td>
<td></td>
<td>---</td>
</tr>
<tr>
<td>Mouse</td>
<td>3</td>
<td>12.3</td>
</tr>
<tr>
<td>Hamster</td>
<td>5</td>
<td>7.4</td>
</tr>
<tr>
<td>Rat</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>Ferret</td>
<td>7</td>
<td>5.3</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Rabbit</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>Dog</td>
<td>20</td>
<td>1.8</td>
</tr>
</tbody>
</table>

### Conversion: example

Conversion of dose in mg/kg to dose in mg/m²

- Human: 1 mg/kg ~ 37 mg/m² (60kg ~ 1.70m²)
- Rat: 1 mg/kg ~ 6 mg/m² (0.15kg ~ 0.03m²)

Conversion of animal dose in mg/kg to HED in mg/kg

6.2 mg/kg in rats is equivalent to 1 mg/kg in humans
Step 3: Most appropriate species selection

- In the absence of data on species relevance the most sensitive species is chosen (i.e., the species with the lowest HED)

- Obligatory: tox data (2 weeks) in 2 species: 1 nonrodent
  (often dog and rat/mouse)
Selection of Maximum Recommended Starting Dose
for drugs administered systemically to normal volunteers

Step 1: Determine NOAELs (mg/kg) in toxicity studies

Is there reason to believe that toxic doses do not scale by body surface area?

- Yes
- No

Step 2: Convert each animal NOAEL to Human Equivalent Dose (HED) (based on body surface area)

HED (mg/kg) = NOAEL (mg/kg) (or other appropriate normalization)

Step 3: Pick HED from most appropriate species

Step 4: Choose Safety Factor and divide HED

Maximum Recommended Starting Dose (MRSD)

Step 5: Consider lowering dose based on a variety of factors, e.g., the PAD

Step 4: Application of safety factor

- A safety factor is applied to provide a margin of safety because
  - uncertainties due to enhanced sensitivity
  - difficulties in detecting certain toxicities in animals
  - differences in receptor densities or affinities
  - unexpected toxicities
  - interspecies differences in ADME

- The default safety factor is 10

- The default safety factor may be increased or decreased using all available information
Increasing the safety factor

- Steep dose response curve
- Severe toxicities
- Nonmonitorable toxicity
- Toxicities without prodromal indicators
- Variable bioavailability
- Irreversible toxicity
- Unexplained mortality
- Large variability in doses or AUC levels eliciting effect
- Questionable study design or conduct
- Novel therapeutic targets
- Animal models with limited utility

Decreasing the safety factor

- The toxicologic testing is of the highest caliber in both conduct and design
- Most of the time, candidate therapeutics for this approach are members of a well-characterized class with
  - administration by the same route, schedule, and duration
  - similar metabolic profile and bioavailability
  - similar toxicity profiles across all species tested including humans
- Toxicities produced by the therapeutic
  - easily monitored
  - reversible
  - predictable
  - shallow dose-response relationship across the tested species
- NOAEL based on toxicity studies of longer duration compared to the proposed clinical schedule in healthy volunteers (assumption of cumulative toxicity)
Selection of Maximum Recommended Starting Dose
for drugs administered systemically to normal volunteers

Step 1
Determine NOAELs (mg/kg) in toxicity studies

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Choose Safety Factor and divide HED

Maximum Recommended Starting Dose (MRSD)

Step 5
Consider lowering dose based on a variety of factors, e.g., the PAD

Step 5: Consideration of the pharmacological active dose (PAD)

- Compare maximum recommended starting dose (MRSD) to the pharmacologic HED derived from pharmacodynamic models
- If MRSD is higher than this pharmacologic HED, it may be appropriate to decrease the clinical starting dose
- MABEL: minimal anticipated biologic effect level
Safety rules for First in Man dosing

- Don’t give a dose in man → plasma concentrations that were not safe from preclinical data (lowest NOAEL)
- NOAEL based on exposure (AUC) and Cmax
- If no human PK available → correct NOAEL to HED
- If human PK available → guidance on plasma conc (AUC & Cmax)
- Take into account safety factor (10 fold) ~ nature of tox (serious? monitorable?)
- Consider appropriate dose escalation (linear PK?)
- First dose should not be pharmacologically active
- Don’t administer doses in ambulatory setting resulting in concentrations that were not proven safe in house

Risk mitigation in early phase clinical trials

1. Facts on drug development
2. Guidelines for clinical drug development
3. How to choose the first dose in man
4. The first-in-man study in practice
First in man studies

- First study: single ascending dose study (SAD)
- First dose = single dose, pharmacologically not active (lower than MABEL), often <1/50 of NOAEL/HED
- Example of dose steps: 1-2-5-10-25-50-100 mg
- Postdose: In-house observation of 24 h (more if needed)
- Standard safety analysis: blood, urine, blood pressure, electrocardiogram, reported adverse events …
- Decision to move to next higher dose step based on complete safety analysis of previous step

First in man studies

Stopping criteria
- Important adverse events
- NOAEL reached
- Withdrawal of volunteer

After single ascending dose study, 1-2 weeks multiple ascending dose study (MAD)
Take possible drug accumulation into account
First in man studies

Study design
- Double blind, randomized, placebo-controlled
- Cohorts of 8 subjects (6 active, 2 placebo)

For innovative mode of actions including biologicals
- Start with 1 active (+1 placebo)
- Low starting dose
- Take large safety factor if drug is targeting the immune system, particularly if it is an agonist (cf. Tegenero)

Serious adverse events (SAEs) in early phase studies

Survey in Belgian early-phase units 2009-2014

Number of volunteers in studies 18995
Number of possibly drug related SAEs 6

0.032% (3,2/10.000)

Possibly drug related SAEs
- Hallucinations/psychosis 2
- Cardiac arrhythmia 1
- Arthritis 1
- Mild renal function decrease 1
- Steven-Johnson 1
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</tr>
<tr>
<td>non drug related SAEs</td>
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Risk for hospitalisation during early phase study is > 10 x higher for a non drug-related reason than for possibly drug related SAEs

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**non disease related SAEs**

- Traffic accidents: 5
- Alcohol intoxication: 1
- Assault at home: 1
- Fractures (falling): 3
- Knee injury at work: 1
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5. Involvement of hospital pharmacist

Involvement of hospital pharmacists

- Keeping randomization lists
- Member of ethics committee
- Drug storage
- Drug packaging and blinding
- Drug manufacturing according to GMP
- Drug delivery (more in later phase studies)
Risk mitigation in early phase clinical trials

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Yes  (green)
No    (red)

the investigator is responsible
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