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AGAH Workshop
First-in-human trials – What you need to know

Clinical conduct of a first-in-human trial

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Overview

- General considerations and definition of Phase I / First-in-human trials
- Design elements of first-in-humans trials and related procedures
- General and specific safety aspects
- Required facilities and technical equipment
- Qualification of the investigator and clinical trial personnel
- Peculiarities in the clinical conduct of a first-in-human trial
- Interim safety data review / Dose Escalation Meetings
- Discussion

Basic technical requirements

Make sure all technical and legal requirements are observed:

- Fire Protection Ordinance: active and passive fire protection (*Brandschutz*)
- Building security (*Gebäudesicherheit*)
- Operating safety and reliability of operation (*Betriebssicherheit*)
- Hazard alarm system (*Gefahrenmeldetechnik*)

Although these aspects are not limited to facilities for the implementation of a first-in-human trial, they can be of particular importance.



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General safety aspects of first-in-human trials

- As always, the clinical trial is conducted on the basis of GCP, and all ethical and legal requirements and applicable guidelines, which requires certain requirements for the infrastructure of the unit, and the qualification and behavior of the staff.
- For first-in-human trials, some special safety requirements must be put in place which are often only covered in general terms by the applicable rules and guidance documents (“... *appropriate* ...”, “... *immediate access* ...”, “... *trained* ...”).
- In large parts, the Investigator’s medical responsibility is concerned.
- In addition to the increased safety requirements, some additional *special* aspects are to be considered, which arise from the nature of the study and the properties of the investigational medicinal product.

Set-up requirements and qualification of trial personnel of first-in-human trials

There are special requirements concerning the ...

- clinical facilities and technical equipment,
- trial-related procedures,
- qualification, experience and special training of the clinical trial personnel
 - concerning first-in-human trials on general
 - concerning the IMP and special design elements of the trial, in particular.
- ways to deal with an emergency situation
 - acute measures by own personnel
 - treatment by an emergency doctor (important aspects are the period of time until arrival of the emergency physician and distance to the next clinical emergency care unit)

Special requirements may exist for special types of clinical trials

Clinical aspects of first-in-human trials (Section 4.4 of the 2017 EMEA Guideline)

“... Key aspects of the trial should be designed to mitigate ... risk factors:

- Study population
- ***Trial sites***
- First dose
- Route and rate of administration
- Number of subjects per dose increment
- Interval between dosing of subjects within the same cohort
- Dose escalation increments
- Transition to next dose cohort
- Stopping rules
- Allocations of responsibilities for decisions with respect to dosing ...“

Clinical aspects of first-in-human trials (Section 4.4.3 of the 2017 EMEA Guideline)

“First-in-human trials should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early phase trials (i.e. phase I-II and medical staff with appropriate level of training and previous experience of first-in-human studies. They should also understand the investigational medicinal product, its target and mechanism of action. ...“

Clinical aspects of first-in-human trials (Section 4.4.3 of the 2017 EMEA Guideline)

“... Units should have immediate access to equipment and staff for resuscitating and stabilising individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of Intensive Care Unit facilities. Procedures should be established between the clinical research unit and its nearby Intensive Care Unit regarding the responsibilities and undertakings of each in the transfer and care of patients. ...“

Clinical aspects of first-in-human trials (Section 4.4.3 of the 2017 EMEA Guideline)

“ ...First-in-human trials should preferably be conducted ^{*)}as a single protocol at a single site. When different sites are involved this should be justified and an appropriate plan needs to be in place to assure the well-being off all trial participants and to assure an adequate information communication system. ...“

*) N.B.: In contrast, the current revised version of that EMA guidance document mentions the possibility of integrating a first-in-human trial into an umbrella protocol.

Some special requirements for the conduct of a first-in-human trial

- Consideration of *all* preclinical data (toxicology, pharmacology, PK)
- Ensuring that all mandatory preclinical studies have been conducted
(*If certain critical aspects have been identified, some additional preclinical tests may be required prior to the start of the first-in-human trial*)
- Correct selection of the starting dose and definition of adequate dose steps
- Consideration of class effects, if known
- Identification of possible “high-risk“ compounds, and, if applicable, taking additional measures to mitigate risk and ensure subject safety:
 - Consider the novelty of the mechanism of action, the nature of the target, and the existing knowledge concerning the relevance of preclinical models (e.g., animal models)
 - Is the biological effect reversible?
 - Could a possible side effect be adequately monitored (i.e, could it be detected at an early time?)
 - Would a causal treatment be possible in case of an intoxication?

The investigator must be able to assess all these aspects on the basis of his education and experience.

First-in-human trials: **Estimating the maximum safe starting dose** **FDA Guidance for Industry**

- Determine No-Observed-Adverse-Effect Levels (NOAELs) [mg/kg] in toxicity studies in appropriate species,
 - Convert each animal NOAEL to Human Equivalent Dose (HED) based on body surface area,
 - Select lowest HED, or HED from most appropriate species,
 - Choose safety factor (normally “10”),
 - Divide HED by that factor,
- ⇒ ***Maximum Recommended Starting Dose (MRSD)***
- Consider lowering the MRSD based on Pharmacologically Active Dose (PAD) (converted to HED, if it is from an *in vivo* study)
-

First-in-human trials:

**When should an increased safety factor (> 10)
be applied?**

- Steep dose-response curve
- Severe toxicities
- Nonmonitorable toxicity
- Unexplained mortality in animal studies
- Toxicities without advance warning
- Irreversible toxicity
- Variable bioavailability
- Non-linear pharmacokinetics
- Inadequate dose-response data
- Novel targets
- Animal models with limited relevance

First-in-human trials:

The Minimal Anticipated Biological Effective Dose (MABEL)

- The MABEL is the anticipated dose level leading to a minimal biologic effect in humans.
- For “high-risk compounds“, the MABEL approach is recommended.
- The following information should be considered (acc. to EMEA Guideline):
 - target binding and receptor occupancy studies *in vitro* in target cells from human and the relevant animal species,
 - concentration-response curves *in vitro* in target cells from human and the relevant animal species, and dose/exposure-response *in vivo* in the relevant animal species,
 - PK/PD modelling, wherever possible.
- A safety factor may be applied for the calculation of the first dose in human from MABEL.
- The safety factor should take into account criteria of risk.
- When the methods of calculation (NOAEL, MABEL) give different estimations of the first dose in man, the lowest value should be used.



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Special safety requirements of first-in-human trials

- Sufficient qualified personnel must be available.
- Technical emergency equipment and emergency medication must be immediately available and correspond to the current state of science.
- Physicians and study nurses must be adequately trained and prepared for the treatment of emergency situations.
- It is advisable that an emergency physician or doctor with *practical* experience in emergency medicine is present on the profile day.
- During the night following the dosing day, a physician (member of the trial team) must stay inhouse in the vicinity of the ward unit where the subjects stay.
- An emergency call system should be installed in all rooms of the phase-I unit.
- The phase-I unit should be located at a reasonable distance from a hospital of the maximum supply that has a large intensive care station.
- Subjects should never be left alone. Single rooms are to be avoided.
- An alarm plan should be visibly placed at a notice board.

Different levels of risk management

Documents and systems (!) that should be in place at the site of clinical conduct of a first-in-human trial:

Desaster Recovery Plan

Guidance document for the handling of a major catastrophic event (usually includes the averting or mitigation of the economic consequences)

Risk Management Plan

Document analysing various risks (may cover medical and business risks)

Medical Emergency Plan

Document (e.g., SOP), which provides detailed instructions for a specific medical emergency and includes the environment and other procedures.

Alarm Plan

gives concrete information in a concise form, to be visibly placed at a notice board

Design elements of a first-in-human trial

First-in-human trials = Phase-I trials in the strict sense
Early-phase trials = Phase-I trials in a broader sense
single-ascending dose (SAD) trial \Leftrightarrow multiple-ascending dose (MAD) trial
SAD trial = First-in-human trial in the strict sense
MAD trial = First-in-human trial in a broader sense

- Ascending dose groups (escalating doses) with different subgroups of healthy subjects
 - SAD trial: usually 6-9 dose steps
 - MAD trial: less dose steps compared to preceding SAD study
- SAD trial: Placebo control, a common ratio is 3:1 (active compound : placebo)
- Primary objective of the SAD trial: identification of the highest dose that is safe and well-tolerated after single dosing, or confirmation of safety and tolerability of all doses tested
- Primary objective of the following MAD trial: confirmation of safety and tolerability of selected doses under steady-state conditions
- The assessment of the systemic exposure / pharmacokinetics (PK) is also important. During the SAD trial, conduct of “online PK evaluation“ is nowadays state of the art.
- In addition, data on pharmacodynamics (PD) are collected, if possible.

First-in-human trials: **Safety aspects for the clinical conduct**

- Commonly N=8 subjects per dose level: 6 on active compound, 2 on placebo.
- When the IMP belongs to a new substance class, not more than 4 subjects should be dosed on a particular calendar day.
- The time interval between two subsequent administrations should be based on safety considerations.
- A *complete* and thorough appraisal of the results of the current dose step must be performed before the dose can be further escalated:
 - Assessment of safety and tolerability to be based on individual subject data listings and descriptive statistics, where appropriate,
 - Assessment of PD data or surrogate parameters in order to obtain first information on biological effects,
 - Evaluation of the plasma levels of the IMP and its active metabolite(s)
= “Online PK”.

Some definitions of terms relevant to design elements of first-in-human trials

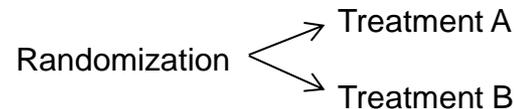
Randomization:

In the statistical theory of design of experiments, randomization involves randomly allocating the experimental units across the treatments or sequences.

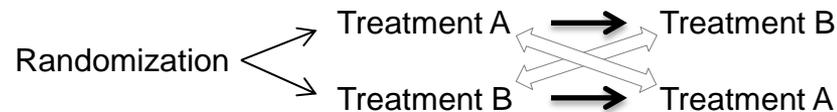
Randomized controlled trial:

Study subjects, after assessment of eligibility and recruitment, but before the intervention begins, are randomly allocated to receive one or other of the alternative treatments or treatment sequences under study.

Parallel-group design:



Crossover design:



Double-blind study:

Experimental procedure in which neither the subjects nor the study personnel know the allocation of treatments. A double-blind procedure is used to minimize bias and placebo-effects.

Some definitions of terms relevant to design elements of first-in-human trials

The design of a first-in-human trial commonly follows a

randomised,
double-blind,
placebo-controlled,
parallel-group (per dose level),
single-dose,
dose-escalation
design

Each dose group *per se* (!) follows a parallel-group design with regard to the random allocation of active compound (applicable dose level) and placebo control to study subjects.

This allocation is usually double-blind, which means that neither the investigational subject, nor the investigator is informed about the assignment.

Sealed emergency envelopes contain the random code and can be opened, if necessary.

The information about the dose group that is going to be investigated in the next step is usually disclosed to the subjects. To put it another way, that information is open-label (This is also because the subjects have to be informed about the results of previous dose groups).

The term “single dose” refers to a particular subject. Each subject will receive one dose only.

Staggering the timing of dosing of clinical investigational subjects

- i) Staggering of the time of dosing of subsequent subjects on a particular study day
- ii) Staggering of subgroups (cohorts) of subjects on different calendar days

Reasons for staggering:

a.) Safety

First-in-human trials:

- limit the number of subjects on a particular study day
- allow sufficient time to see early side effects
interval depends on safety considerations

b.) Logistical aspects

nearly all studies:

- allow for adequate resources during a certain period of time (i.e., avoid too many overlapping procedures)
interval as short as needed to allow for sufficient resources

Staggering the timing of dosing of clinical investigational subjects

Example (First-in-human trial)

PK Blood samples and safety measurements are scheduled at +15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, ...

Four (4) subjects are dosed on a particular profile day.

Subjects will be dosed at 07:00, 07:37, 08:14, 08:51 am.

Blood samples and safety measurements will be performed at:

# 01	# 02	# 03	# 04
07:15	07:52	08:29	09:06
07:30	08:07	08:44	09:21
07:45	08:22	08:59	09:36
08:00	08:37	09:14	09:51
08:30	09:07	09:44	10:21
09:00	09:37	10:14	10:51
10:00	10:37	11:14	11:51
11:00	11:37	12:14	12:51

More than two overlapping measurements should be avoided.

A possible schedule of a First-in-human trial with ascending dose groups and staggered sub-groups per dose group (excerpt)

Date	Dose Group 1 1st subgroup	Dose Group 1 2nd subgroup	Dose Group 2 1st subgroup	Dose Group 2 2nd subgroup
01 Saturday				
02 Sunday	Admission (evening)			
03 Monday	Dosing of N=4			
04 Tuesday	↓	Admission (evening)	Information of subjects	Information of subjects
05 Wednesday	↓	Dosing of N=4		
06 Thursday	Discharge	↓	Screening examination	
07 Friday	Start of bioanalytics	↓		
08 Saturday		Discharge		
09 Sunday				
10 Monday		Start of bioanalytics		Screening examination
11 Tuesday				
12 Wednesday				
13 Thursday			Results of Online PK available	
14 Friday			Dose Escalation Meeting (or TC)	
15 Saturday				
16 Sunday			Admission (evening)	
17 Monday			Dosing of N=4	
18 Tuesday			↓	Admission (evening)
19 Wednesday			↓	Dosing of N=4
20 Thursday			Discharge	↓
21 Friday			Start of bioanalytics	↓
22 Saturday				Discharge
23 Sunday				
24 Monday				Start of bioanalytics

Pharmacodynamic (PD) endpoints as secondary endpoints in first-in-human trials

- First-in-human trials are usually described as studies on safety and tolerability, with PD being a secondary objective, because safety aspects are prevailing
- In phase-I trials, additional parameters for the assessment of the compound's pharmacodynamic effects are commonly added as secondary endpoints, if feasible.
Examples:
 - Reduction of airway resistance by inhaled b2-adrenergics can, in fact, be measured in healthy subjects by body plethysmography
 - Reduction of the intragastric pH-value by proton pump inhibitors can be measured in healthy subjects but requires semi-invasive methodology which might not be appropriate in a first-in-human trial
- Whether or not a desired clinical effect of an investigational compound can be measured in healthy subjects depends on the mechanism of action and target.
- Many physiological parameters can hardly be influenced in healthy subjects because certain mechanisms of counterregulation come into action (example: blood pressure).
- However, at the biochemical level, some drug effects are detectable even in healthy subjects (*e.g.*, effect on biomarkers, inhibition of enzymes).

Combination of a first-in-human trial with a food-effect trial

- The effect of food intake on the extent and rate of absorption of an orally administered drug should be investigated as early as possible ...
 - to optimize dose finding, and
 - to ensure optimal food recommendations in clinical studies and drug labelling.
- Especially lipophilic drugs may be prone to food interaction. The systemic exposure may increase by factor 3, and that is why a food interaction may be safety-relevant.
- The effect of a high-fat meal on the absorption of the investigational drug should be investigated as the worst-case scenario.
A single dose of the drug is administered with 240 mL of water after a 10-hour fasting period and 30 minutes after intake of a standard meal has been started.
- The results are compared to the situation in fasted state.
- Food-effect trials are usually conducted according to a two-period (*fed / fasted*) crossover design.
- When a food-effect trial is combined with a first-in-human trial, the food-effect trial part may either be added at the end of the dose escalation, or an interim dose level may be selected for that investigation.

Design aspects of multiple-ascending dose (MAD) safety trials

(i.e., the first clinical trial following the SAD trial)

- The design of the MAD study shall be based on the results of the SAD study. This applies to the dose escalation scheme and the time schedule of safety, PK and PD measurements which should be optimized on the basis of the PK profiles and/or safety findings.
N.B.: This is an argument against the combination of SAD part and MAD part in one and the same umbrella protocol
- The number of dose steps is usually lower than in the SAD study (commonly three).
- The number of subjects per dose step is usually higher than that in the SAD study, e.g., N=12: 9 subjects on active compound, 3 on placebo.
- The highest dose step of the MAD study is usually lower than the highest dose step of the SAD study taking into account steady-state conditions and chronic exposure.
- *A complete* evaluation of the safety and tolerability results of each dose group should be performed prior to dose escalation.
- A risk of sensitization due to multiple dosing must be considered, particularly for biologics.



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Recruitment of healthy subjects for a first-in-human trial

- Some special inclusion/exclusion criteria apply.
- A sufficient number of subjects should be screened to make sure enough subjects will fulfill the entry criteria.
- Clinical safety laboratory investigation must be performed within three days prior to planned dosing (lab must be repeated, if screening was done earlier)
- On each dosing day, a spare subject (*Ersatzproband*) should be invited to be waiting at the study site until the last subject will have been dosed.
- For a first-in-human trial, it is advantageous when the study participants have participated in any other clinical trial at the site before.

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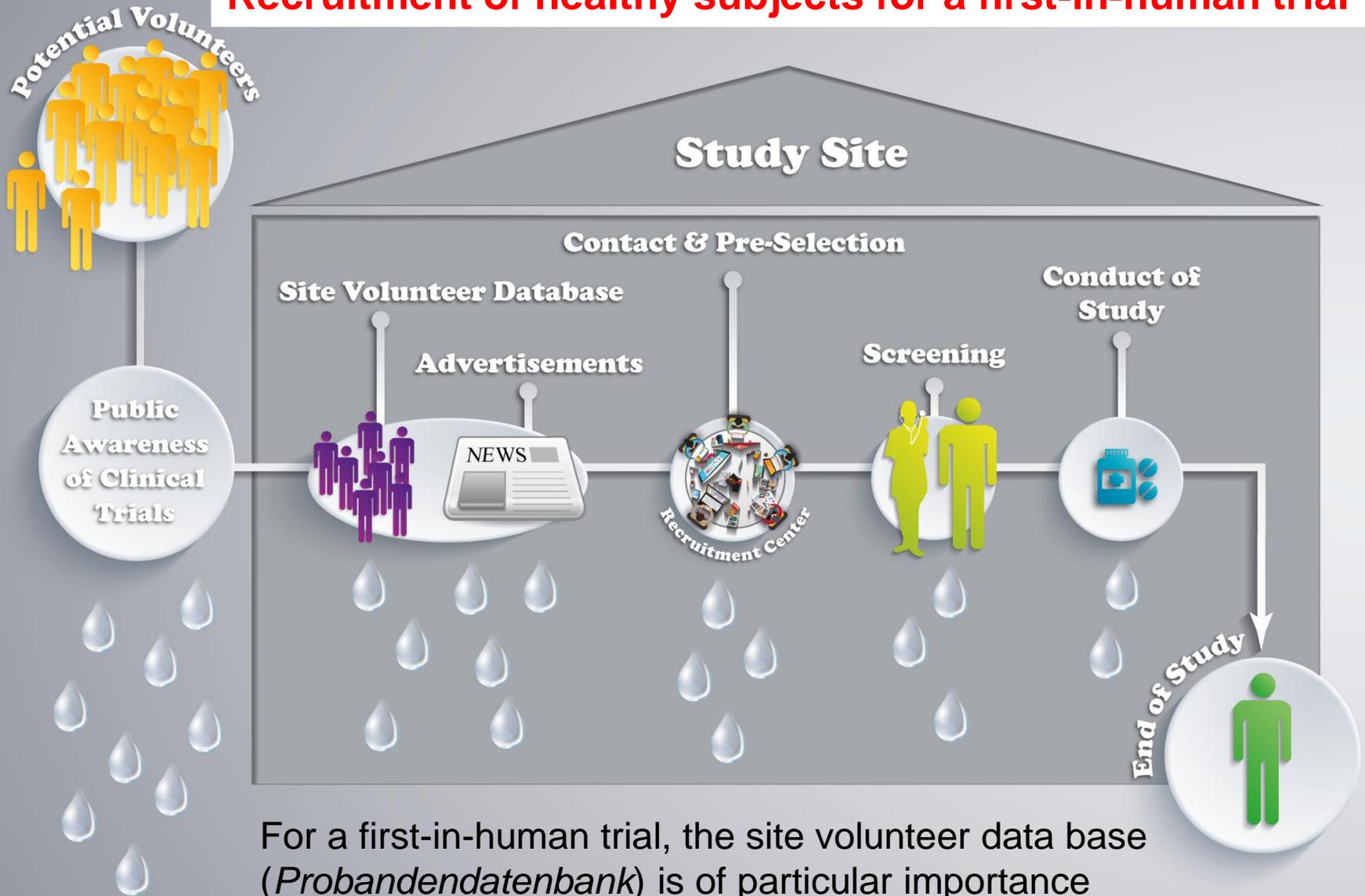
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Die Inamed GmbH, ein etabliertes Auftragsforschungsinstitut in der Nähe von München, sucht für klinische Studien laufend Probanden im Alter ab 18 Jahren.

- Patienten mit Asthma
- Patienten mit chronischer Bronchitis (COPD)
- Patienten mit Mukoviszidose (Zystische Fibrinose)

Ärztliche Betreuung und Medikamentenversorgung im Rahmen der jeweiligen klinischen Prüfung erfolgt kostenlos. Der zeitliche Aufwand wird je nach Studie unterschiedlich erstattet. Alle Studien und damit verbundene Untersuchungen sind den Behörden angezeigt und genehmigt.

Recruitment of healthy subjects for a first-in-human trial



For a first-in-human trial, the site volunteer data base (*Probandendatenbank*) is of particular importance



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Guided tour of a phase-I unit





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Clinical unit with bedrooms, measuring rooms and labs





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Doctor's room





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Bedrooms for overnight stay





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Radio-controlled clocks in all rooms

(additional functions required for calibration of medical equipment)





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Emergency
button

Infrastructure – Emergency call system

- Possibility to trigger a central alarm by study participants in the rooms and sanitary areas and by assistant staff in the measuring rooms
- Loud acoustic signal that can heard in the entire clinical unit
- Optical display (locally and centrally)
- Alternatively, subjects may be given cell phones to call the investigator on duty by pressing any key
- Availability of telephones at accessible places for external phone calls, clearing of an emergency call number



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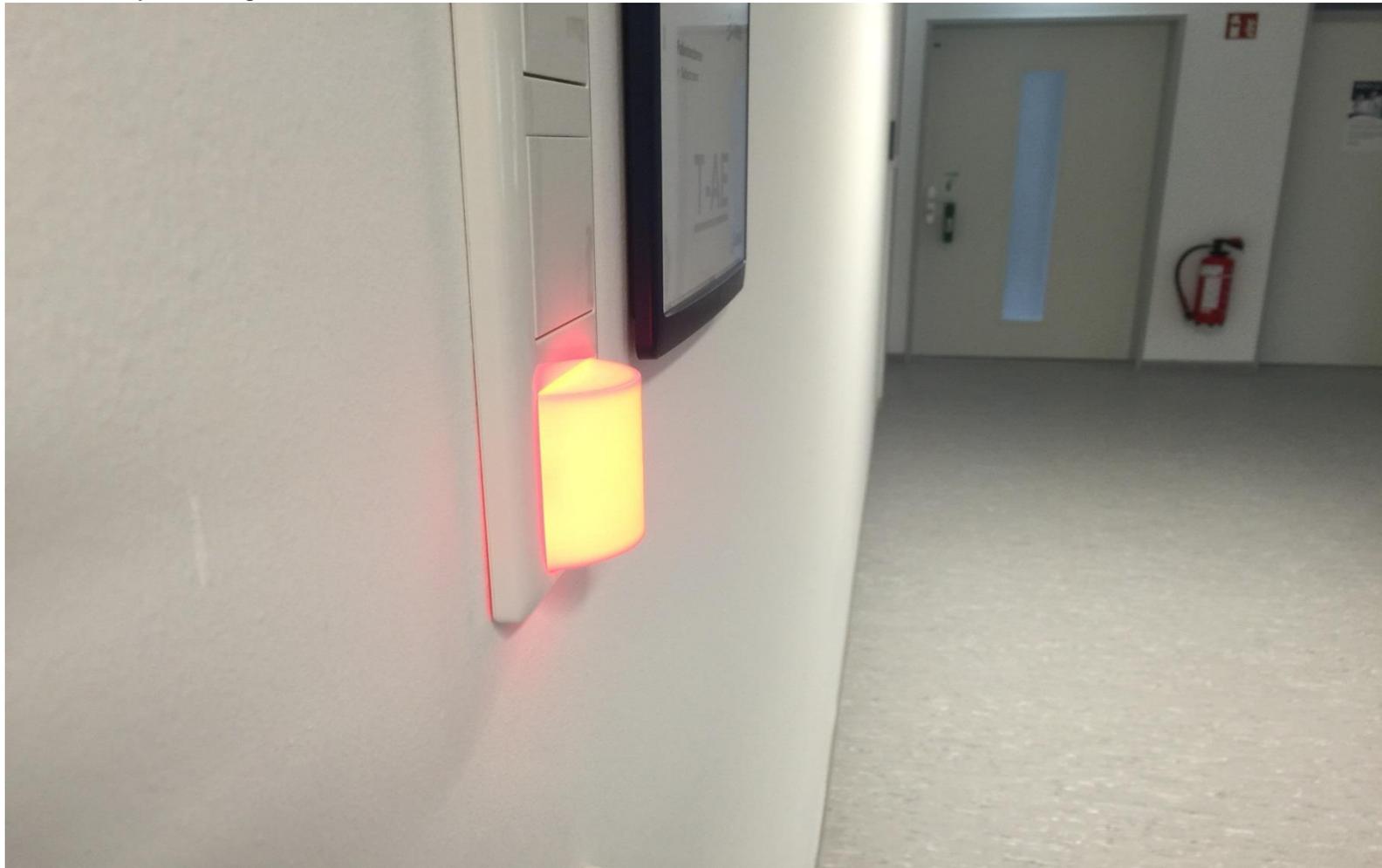
Emergency button





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Optical (and audible) alarm display





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Infrastructure – Measuring room for first-in-human trials (Intensive Monitoring Unit)





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Infrastructure – Measuring room for first-in-human trials (intensive monitoring unit)



- Bedside monitoring of all important vital parameters (e.g., by Draeger monitors)
- All monitors are connected with central monitoring unit
- Adjustable alarm functions
- Equipment for different modes of administration (e.g., i.v.-dosing with controlled flow rate ^(*))

^(*) Labs for manufacturing of individual trial medication by Qualified Person (QP, Pharmacist) should also be available

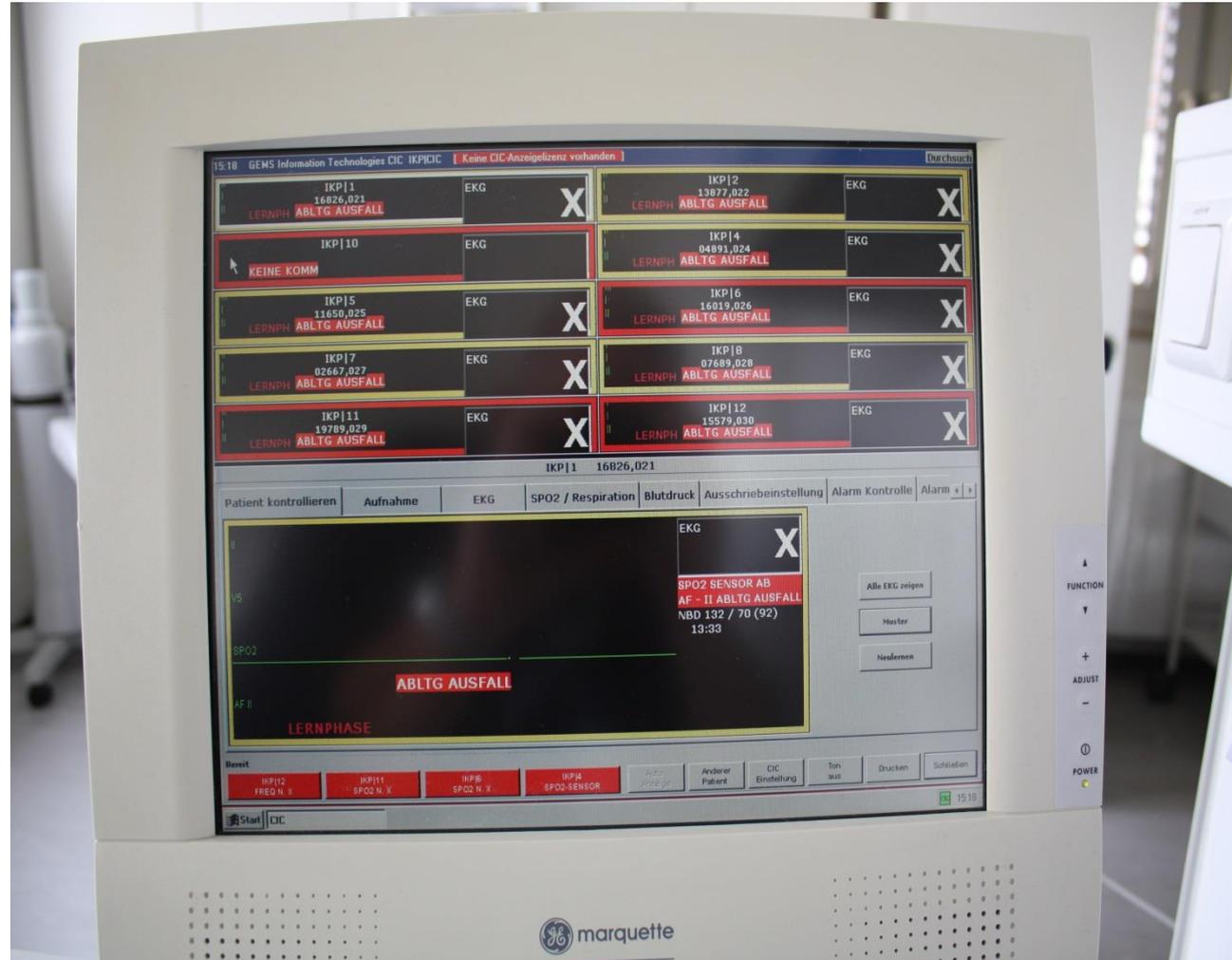


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Infrastructure – Central Monitoring Unit

- Simultaneous supervision of several beds
- adjustable alarm functions
- Monitoring of various vital parameters





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Infrastructure – Bedside monitor (Dräger® system)





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Multifunctional room

used for different examinations or blood samplings





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Lab area / multifunctional room used for processing of blood samples





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Lab area / sink made of stainless steel
used for (e.g.) urine PK trials





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Measuring room

e.g., body plethysmography





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Recreational area for study participants also used as waiting area

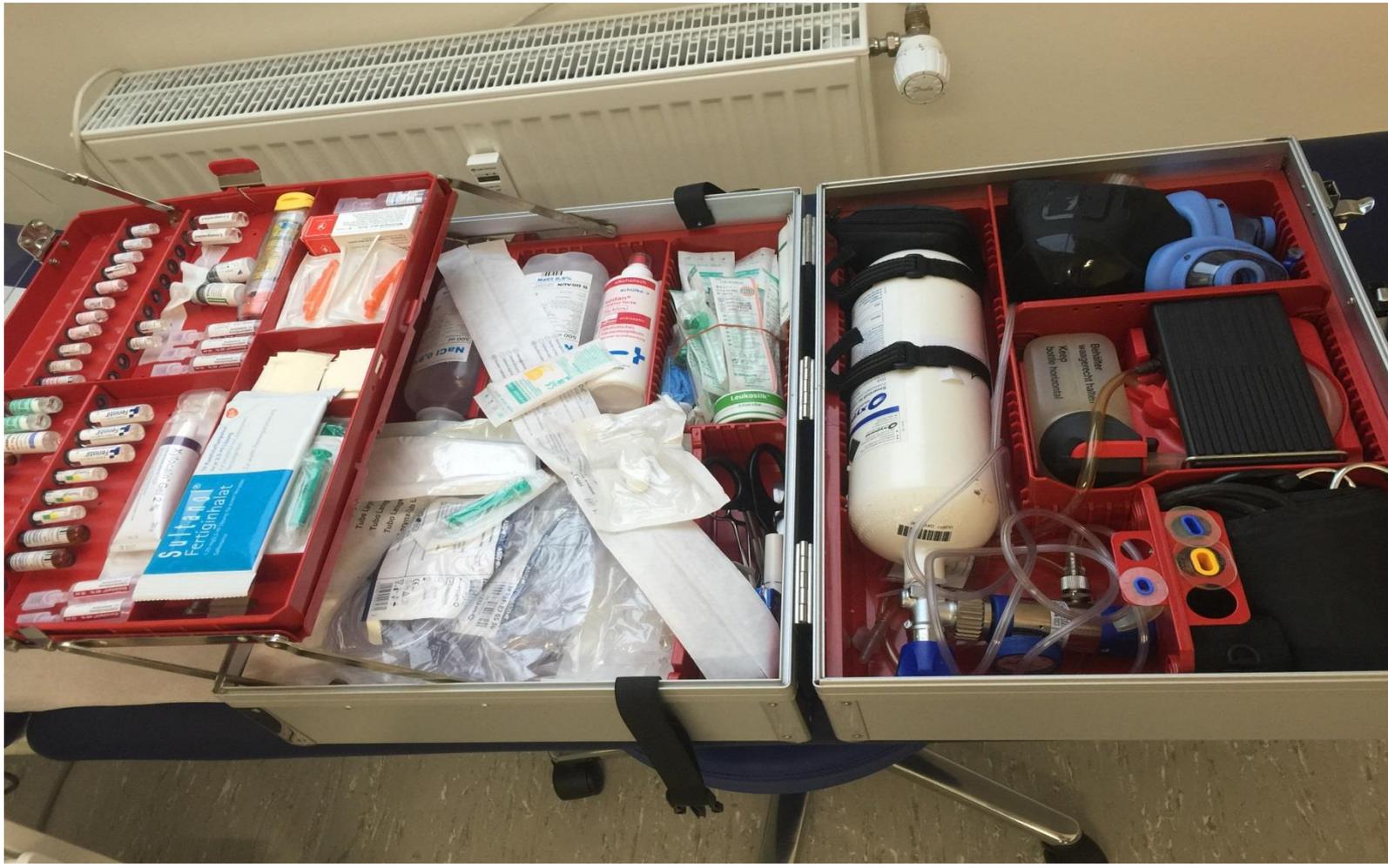


Emergency Medication and Equipment

- Semi-automatic defibrillator with the function of ECG monitoring
- Emergency medication according to current recommendations
- Intubation set, tubus, masks for respiration, oxygen supply
- Syringes, solvents, medical gloves, NaCl, Aqua ad. inj., etc.
- Blood pressure meter
- Inspection and maintenance in regular intervals (to be documented)



Emergency Medication and Equipment



Infrastructure – Securing access to emergency equipment and rescue routes

- In case the clinical unit is distributed over several levels in the building, a complete set of emergency equipment should be located at every level.
- Ideally, several sets of emergency equipment exist per floor level, if the study is conducted in several rooms, or if there are long hallways.
- An elevator installation should be available in order to secure the study operation and transport route (however, healthy subjects should not use the lift).
- The access route of the ambulance must be clear (see medical emergency plan / alarm plan).
- Opening of the doors must be possible at all times.
- Wide doors that allow transport of patients in supine position.
No tight and winding rooms!
- Escape routes must also be open to study participants (with simultaneous door control, i.e., a door alarm will be released in case of unauthorized exit).

Medical Emergency Plan

A Phase I unit has a Medical Emergency Plan whose content is regularly trained in addition to general and special emergency measures :

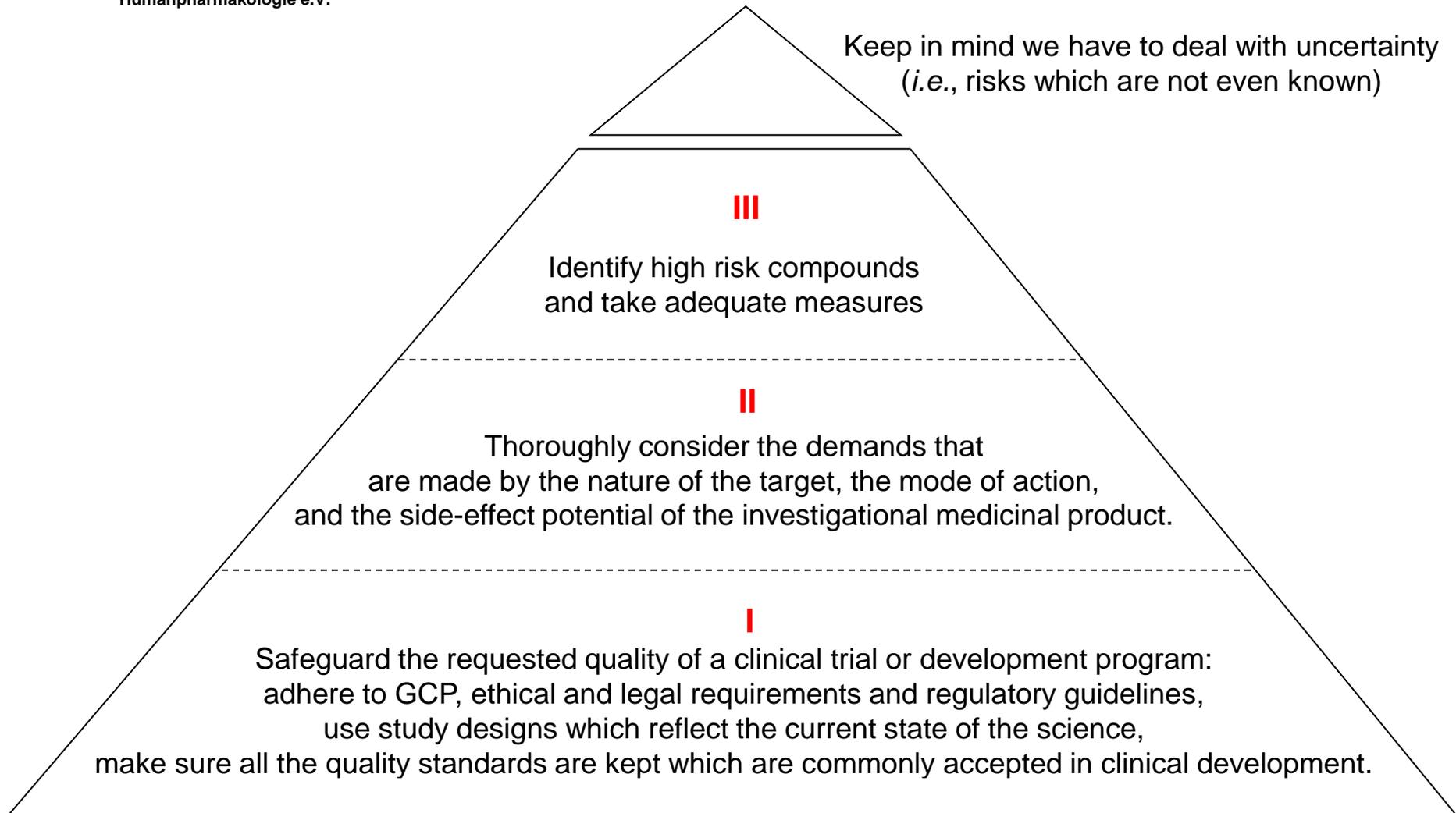
- Who will take over what function?
- What's the emergency number?
- What else has to be done?
- Who opens the doors?
- Where are the keys?
- Where are the emergency envelopes?
- How to ensure that the attending physician receives sufficient oral and written information?

etc

In a Phase I unit, the Medical Emergency Plan has the importance of an SOP.

Minimisation of risk during clinical conduct of a first-in-human trial

Keep in mind we have to deal with uncertainty
(*i.e.*, risks which are not even known)



Some special requirements for the conduct of a first-in-human trial

There are logistical requirements that apply to all studies, but are particularly important for first-in-human trials, e.g., ...

- Ensuring that the subjects have not recently participated in another clinical trial,
- Overview of important information from previous clinical trials, in the form of a subject master file or database,
- Monitored daily routines, even after the end of the period of intensified monitoring,
- Standardization of all study procedures, preparation of standard meals,
- Separation of subjects from different studies in separate ward units,
- Follow-up visit and telephone availability after discharge

Period of intensified safety monitoring following dosing in first-in human trials

- Continuous monitoring of vital parameters for at least 5 hours: 3-lead ECG, blood pressure, pulse, respiration rate, oxygen saturation in peripheral blood
- Period of intensified safety monitoring may also depend on the half-life of the drug and the duration or nature of the pharmacodynamic effect
- At least two physicians are needed in the measuring room in the morning of the profile day, at least until all subjects have been dosed:
 - One investigator needed for dosing and immediate medical assessments of safety measurements and adverse events recording
 - Another investigator needed exclusively for continuous monitoring of vital parameters (may be seated in front of the central monitor)

Integrated safety review after each dose group, and review of systemic exposure data (“online PK“)

- Complete review and assessment of all safety-relevant results of a particular dose group prior to proceeding to the next higher dose:
 - Safety and tolerability data of all subjects,
 - Pharmacodynamic data, if applicableindividual subject data listings; summary statistics if needed

Ad hoc-compilation of the key results after each dose step,
Review and assessment by experts (Investigator, clinical pharmacologist,
biostatistician if needed, external experts if requested)
Conduct of a Dose Escalation Meeting.

- Evaluation of the plasma levels (systemic exposure) of the investigational compound and relevant metabolites („Online PK“).

Quick shipment of plasma samples to bioanalytical lab (ideally, the testing facility has its own bioanalytical lab or is connected to a bioanalytical lab).
Review and assessment of online PK data by experts (clinical pharmacologist, pharmacokineticist) during the Dose Escalation Meeting

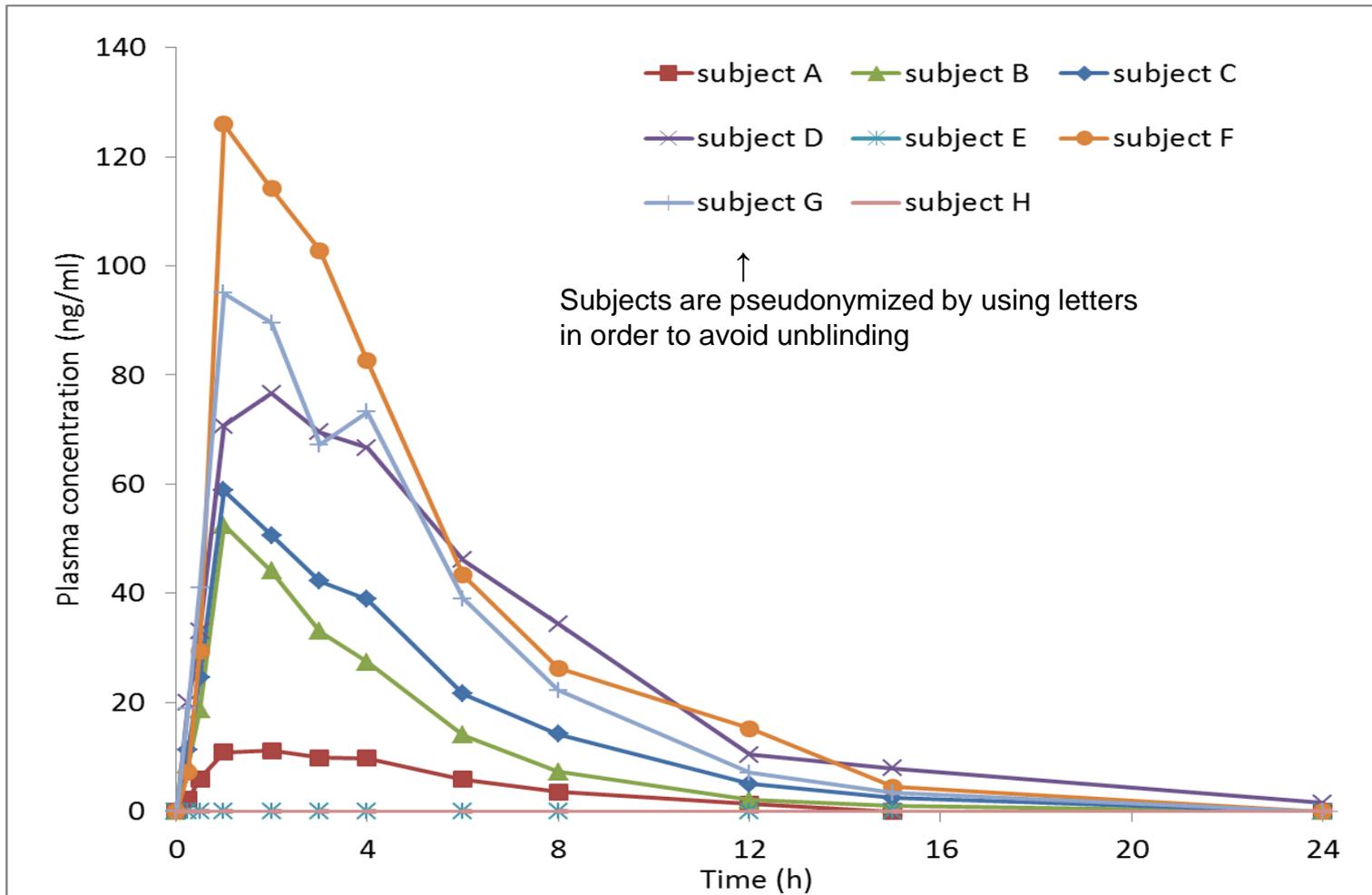
Presentation of Key Safety Results for Dose Escalation Meeting – Example

Vital signs												
RND	Visit	Date & Time	Dose	after 10 min rest in supine position				after 3 min in standing position			Transcribed by	Double checked by
				RR syst.	RR dias.	HR	Temp.	RR syst.	RR dias.	HR		
001	Day -21 to -3 (Screening)	20.07.2015,08:17	20 mg	131	86	69	36,6	117	88	82	RP	MN
	Day 1 / predose	27.07.2015, 07:28	20 mg	126	86	70	36,4	118	92	92	RP	MN
	Day 1 / 1h post	27.07.2015, 08:55	20 mg	123	85	73	36,2	116	92	83	RP	MN
	Day 1 / 2h post	27.07.2015, 09:54	20 mg	124	84	69	36,0	121	86	82	RP	MN
	Day 1 / 4h post	27.07.2015; 11:52	20 mg	118	78	67	36,3	126	86	80	RP	MN
	Day 1 / 8h post	27.07.2015, 15:54	20 mg	117	74	70	36,7	124	86	87	RP	MN
	Day 1 / 12h post	27.07.2015, 19:52	20 mg	119	78	73	36,5	126	93	87	RP	MN
	Day 2 / 24 post	28.07.2015, 07:52	20 mg	120	77	65	36,5	133	87	93	RP	MN
	Day 6 to 9 (Follow up)	03.08.2015, 07:30	20 mg	130	81	64	35,9	126	85	79	MN	HU
RND	Visit	Date & Time	Dose	after 10 min rest in supine position				after 3 min in standing position			Transcribed by	Double checked by
				RR syst.	RR dias.	HR	Temp.	RR syst.	RR dias.	HR		
002	Day -21 to -3 (Screening)	22.07.2015, 09:26	20 mg	117	65	62	36,4	125	82	81	RP	MN
	Day 1 / predose	27.07.2015, 07:44	20 mg	119	70	55	36,5	103	98	89	RP	MN
	Day 1 / 1h post	27.07.2015, 09:16	20 mg	110	70	59	36,6	98	64	79	RP	MN
	Day 1 / 2h post	27.07.2015, 10:13	20 mg	112	66	60	36,3	114	86	78	RP	MN
	Day 1 / 4h post	27.07.2015, 12:14	20 mg	120	74	61	36,8	114	78	76	RP	MN
	Day 1 / 8h post	27.07.2015, 16:13	20 mg	98	54	50	37,1	97	73	108	RP	MN
	Day 1 / 12h post	27.07.2015, 20:12	20 mg	114	60	57	36,4	109	70	91	RP	MN
	Day 2 / 24 post	28.07.2015, 08:17	20 mg	112	58	56	36,4	95	72	92	RP	MN
	Day 6 to 9 (Follow up)	03.08.2015, 08:45	20 mg	113	60	57	36,2	114	79	91	MN	HU

Presentation of Key Safety Results for Dose Escalation Meeting – Example

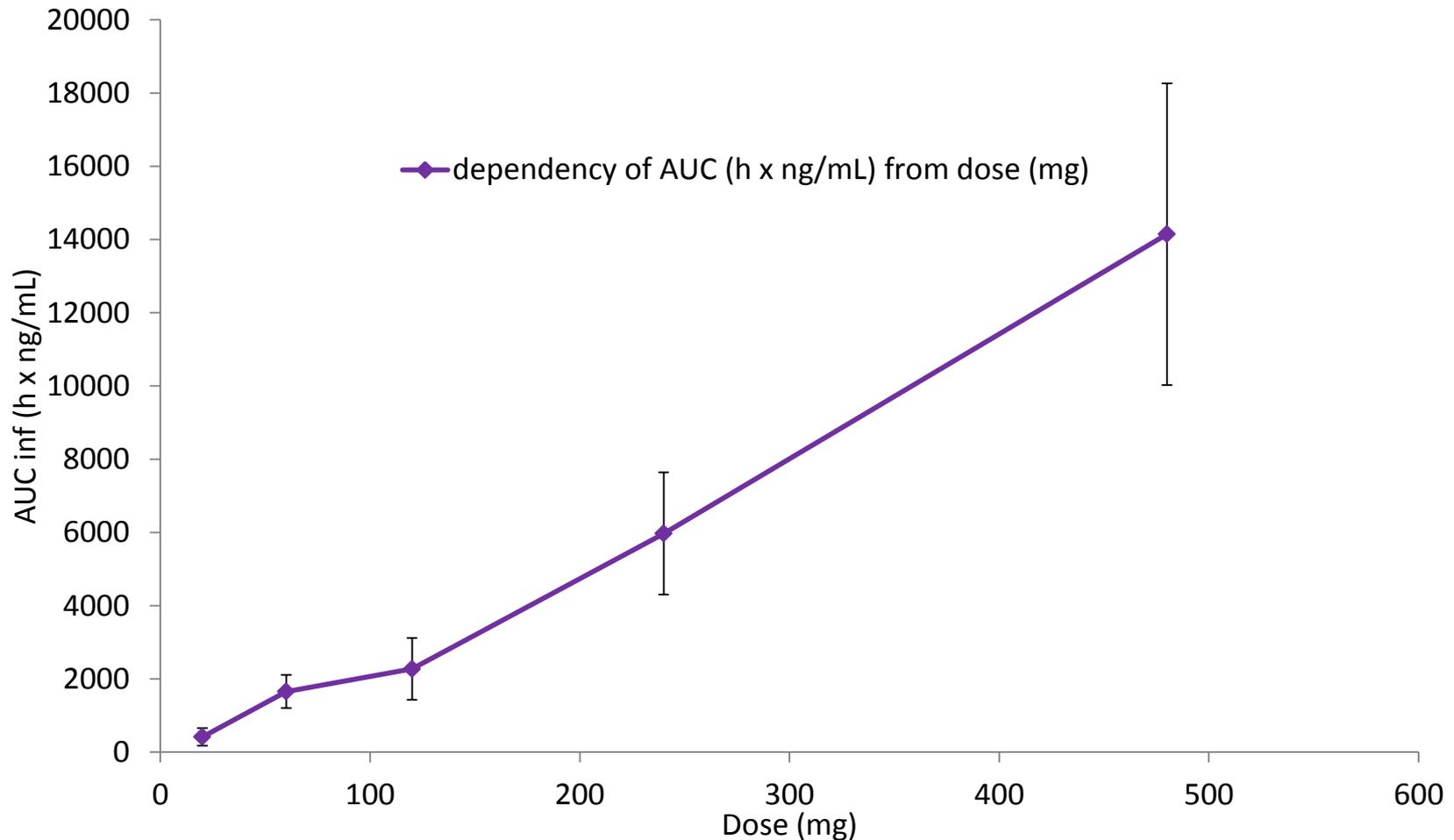
Safety Lab: relevant deviations in red									
Value	RND	Range (male)	Day -21 to -3 (Screening)	additional lab Screening	predose Day 1	Day 2	Day 6 to 9 (Follow up)	Transcribed by	Double-checked by
Bilirubin	001	0.30 - 1.20 mg/dl	0,46	0,64	0,51	0,75		RP	MN
Bilirubin	002	0.30 - 1.20 mg/dl	0,43		0,59	0,92		RP	MN
Bilirubin	003	0.30 - 1.20 mg/dl	0,63		0,68	1,39		RP	MN
Bilirubin	004	0.30 - 1.20 mg/dl	0,94		0,68	0,98		RP	MN
Bilirubin	005	0.30 - 1.20 mg/dl	0,6	1,07	0,54	1,25		RP	MN
Bilirubin	006	0.30 - 1.20 mg/dl	0,73	0,29	0,47	0,8		RP	MN
Bilirubin	007	0.30 - 1.20 mg/dl	0,63	0,71	0,58	1,26		RP	MN
Bilirubin	008	0.30 - 1.20 mg/dl	0,39	0,45	0,4	0,71		RP	MN
TSH	001	0.55 - 4.78 µU/ml	1,61	1,996	1,57	1,565		RP	MN
TSH	002	0.55 - 4.78 µU/ml	2,041		1,992	1,368		RP	MN
TSH	003	0.55 - 4.78 µU/ml	1,35		2,171	1,432		RP	MN
TSH	004	0.55 - 4.78 µU/ml	1,521		1,635	1,377		RP	MN
TSH	005	0.55 - 4.78 µU/ml	1,741	2,428	1,145	1,543		RP	MN
TSH	006	0.55 - 4.78 µU/ml	1,169	2,739	1,368	0,908		RP	MN
TSH	007	0.55 - 4.78 µU/ml	0,556	2,609	1,39	0,759		RP	MN
TSH	008	0.55 - 4.78 µU/ml	1,617	2,658	1,219	1,944		RP	MN
Serum Creatinine	001	0.70 - 1.30 mg/dl	0,87	0,9	0,8	0,96		RP	MN
Serum Creatinine	002	0.70 - 1.30 mg/dl	0,82		0,91	0,85		RP	MN
Serum Creatinine	003	0.70 - 1.30 mg/dl	0,88		0,62	0,93		RP	MN
Serum Creatinine	004	0.70 - 1.30 mg/dl	0,87		0,68	0,87		RP	MN
Serum Creatinine	005	0.70 - 1.30 mg/dl	0,79	0,9	0,78	0,91		RP	MN
Serum Creatinine	006	0.70 - 1.30 mg/dl	0,82	0,84	0,83	0,92		RP	MN
Serum Creatinine	007	0.70 - 1.30 mg/dl	0,78	0,96	0,86	0,97		RP	MN
Serum Creatinine	008	0.70 - 1.30 mg/dl	0,89	1,07	0,91	1,01		RP	MN

Online PK Evaluation – Example



Online PK Evaluation – Example

Here: Assessment of dose linearity by comparing AUC as a measure of systemic exposure across different dose groups



Dose Escalation Meeting Minutes – Example

	<p>Sponsor Study Code: ... (Inamed Study Code: ...)</p> <p>Dose Escalation Meeting Minutes Drug Safety Data Monitoring Committee (DMC) Meeting Minutes</p>	<p>FM R-AA-06 Version: Final 01 Page 1 / 7</p>
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EudraCT No.:	...			
Sponsor protocol code:	...			
Investigational Product:	...			
Title:	Phase-I study in healthy subjects to investigate safety, tolerability and pharmacokinetics of orally inhaled single-doses of ... – A randomised, double-blind, placebo-controlled, parallel-group (per dose level) dose-escalation study of inhaled single doses.			
Date of meeting:	21.08.2015			
No. of dose group / cohort:	2	Dose: 60mg ... in 4 ml solution or matching placebo		
Demographics	Subject No.: 09	Subject No.: 10	Subject No.: 11	Subject No.: 12
Age:	35 years	27 years	35 years	26 years
Gender:	male	male	Male	male
Weight:	75.5 kg	76.6 kg	77.3 kg	72.8 kg
Demographics	Subject No.: 13	Subject No.: 14	Subject No.: 15	Subject No.: 16
Age:	24 years	37 years	24 years	31 years
Gender:	male	male	Male	male
Weight:	72.1 kg	79.5 kg	76.0 kg	59.4 kg (Remark: 60.1 kg at screening)

Dose Escalation Meeting Minutes – Example

	Sponsor Study Code: ... (Inamed Study Code: ...)	FM R-AA-06 Version:Final 01 Page 2 / 7
	Dose Escalation Meeting Minutes Drug Safety Data Monitoring Committee (DMC) Meeting Minutes	

Summary of Key Safety Results:				
Where there any SAEs?				
<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes	
<i>If yes, please refer to the Excel sheet with the Key Safety Results Attach SAE Report(s) to these meeting minutes, if applicable. Provide further important information below:</i>				
Where there any AEs?				
<input type="checkbox"/>	No	<input checked="" type="checkbox"/>	Yes, but AEs were clinically not significant and remained within the scope of AEs usually observed in clinical trials	
		<input type="checkbox"/>	Yes, clinically significant AEs occurred	
<i>If yes, please refer to the Excel Sheet with the Key Safety Results Provide further information on clinically significant AEs below, if applicable:</i>				
<p>Even though they are not regarded as clinically significant, some further information to the two AEs that were reported in this dose group are given in the following:</p> <p>Subject No. 10 reported a short episode of mild weakness at approximately 1h after end of inhalation, when he got up and went to the toilet being accompanied by the investigator. That subject had a relatively low blood pressure already at predose. That constellation may probably be explained by the study conditions (e.g., no breakfast) and environmental conditions (entering warm floor after having left the air-conditioned Intensive Monitoring Unit).</p> <p>Subject No. 16 reported a mild feeling of irritation in the upper airways which lasted for approximately one hour after inhalation. During that period of time FEV1 tended to decrease a little (83% FEV1 of predicted at 0.5h) which was not regarded as clinically significant, but may possibly be related to the preceding inhalation procedure (not necessarily to the investigational compound itself). No further respiratory symptoms occurred.</p>				

Dose Escalation Meeting Minutes – Example

	<p>Sponsor Study Code: ... (Inamed Study Code: ...)</p> <p>Dose Escalation Meeting Minutes Drug Safety Data Monitoring Committee (DMC) Meeting Minutes</p>	<p>FM R-AA-06 Version: Final 01 Page 3 / 7</p>
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Where there any other safety or tolerability findings (clinically significant abnormal values or clinically relevant change) in the following safety assessments?				
Vital signs	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please refer to the Excel Sheet</i></p> <p><i>Provide further important information below, if applicable:</i></p>				
ECG	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please refer to the Excel Sheet.</i></p> <p><i>Provide further important information below, if applicable:</i></p>				
Physical examination (including heart and lung auscultation)	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please specify per subject:</i></p>				
Clinical laboratory values	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please refer to the Excel Sheet</i></p> <p><i>In case of clinically significant alterations of a particular clinical laboratory parameters during the course of the study, the entire time course of the concerned parameter should be listed on the excel sheet in the respective subject(s).</i></p> <p><i>Provide further important information below, if applicable:</i></p>				

Dose Escalation Meeting Minutes – Example

	<p>Sponsor Study Code: ... (Inamed Study Code: ...)</p> <p>Dose Escalation Meeting Minutes</p> <p>Drug Safety Data Monitoring Committee (DMC) Meeting Minutes</p>	<p>FM R-AA-06 Version: Final 01 Page 4 / 7</p>
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Lung function measurements	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please refer to the Excel Sheet:</i></p> <p><i>Provide further important information below, if applicable:</i></p> <p>Even though not regarded as clinically significant, some further information to one short episode of mild drop of FEV1 is given in the following:</p> <p>Subject No. 16 reported a mild feeling of irritation in the upper airways which lasted for approximately one hour after inhalation. During that period of time FEV1 tended to decrease a little (83% FEV1 of predicted at 0.5h) which was not regarded as clinically significant, but may possibly be related to the preceding inhalation procedure (not necessarily to the investigational compound itself). No further respiratory symptoms occurred.</p> <p><i>(same comment as to "adverse events" above)</i></p>				

In summary, were there any safety findings that have implications for the dosing of the next cohort(s)?				
	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes
<p><i>If yes, please specify below:</i></p>				

Dose Escalation Meeting Minutes – Example

	<p>Sponsor Study Code: ... (Inamed Study Code: ...)</p> <p>Dose Escalation Meeting Minutes Drug Safety Data Monitoring Committee (DMC) Meeting Minutes</p>	<p>FM R-AA-06 Version: Final 01 Page 5 / 7</p>
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Assessment of PK Results / Systemic Exposure					
Please refer to the Online PK Tables and Figures as provided by ...					
<i>Describe important observations (e.g., high variability, individual subjects with extraordinary high plasma concentrations, biphasic PK profiles) below, if applicable:</i>					
Reasonable concentration-time profiles were detectable in 6 of 8 subjects. See "PK Data-Reviewer" provided by ... with the (anonymized) plasma PK data of the second dosing group.					
<i>For the higher dose groups: Did the systemic exposure (extent and rate of absorption) observed at the current dose level increase more than dose-proportionally?</i>					
<i>Refer to dose-normalized AUC- and C_{max}-ratios on the Online PK Tables and Figures and the summary illustration of the PK profiles of the current dose group and all previous dose groups.</i>					
	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes	
Remark: A valid statement on dose-proportionality cannot be made based on the data of the two lowest dose groups only, however, C _{max} and AUC did not obviously appear to increase more than dose-proportionally when the nominal dose was increased from 20 mg to 60 mg.					
<i>Taking into account the available PK data from the present study, and the results of the safety and tolerability information obtained so far, and all available non-clinical exposure data from animal pharmacology studies (e.g., toxicokinetics), are there any hints that the systemic exposure (extent and rate of absorption) to be expected in the next dose group (dose escalation acc. to protocol) will pose a safety risk?</i>					
<i>In case of high variability, the possibility of high plasma concentrations in individual subjects should also be taken into account.</i>					
	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes	
If yes, what is the possible safety issue, and which measures will be taken?					
In summary, does the online evaluation of PK data have any implications for the further study conduct?					
	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>	Yes	

Dose Escalation Meeting Minutes – Example

	<p>Sponsor Study Code: ... (Inamed Study Code: ...)</p> <p>Dose Escalation Meeting Minutes</p> <p>Drug Safety Data Monitoring Committee (DMC) Meeting Minutes</p>	<p>FM R-AA-06 Version: Final 01 Page 6 / 7</p>
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If yes, which implications?

Summary Statement:	<p>A summary of important key safety results is given below:</p> <p><i>According to DMC Charta, a brief rationale for the recommendations to terminate or suspend/modify the study/dose is to be presented in the summary statement. If the dose level was assessed to be safe and well tolerated and the recommendation is to continue the trial as planned, no detailed rationale is required. If there are any matters of concerns that require due consideration in the next dose group, they should be described in detail. Moreover, any decision to modify the study/dose should be explained in detail, if applicable.</i></p> <p>Tick, if applicable</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30px; text-align: center; vertical-align: top;"><input checked="" type="checkbox"/></td> <td style="padding: 2px;">Will the study be continued as planned acc. to protocol? What is the next dose level to be administered in the next dose group? 120 mg ... in 4 ml solution or matching placebo</td> </tr> <tr> <td style="text-align: center; vertical-align: top;"><input type="checkbox"/></td> <td style="padding: 2px;">Will the study be prematurely terminated?</td> </tr> <tr> <td style="text-align: center; vertical-align: top;"><input type="checkbox"/></td> <td style="padding: 2px;">Will the study be modified, e.g., will an interim dose level be investigated in the next cohort? If yes, specify:</td> </tr> </table> <p><i>Add further summary statement here, if applicable:</i></p> <p>The dose level of 60 mg ... was assessed to be safe and well-tolerated.</p> <p><u>Action Items:</u></p> <p>DMC Chairman Prof. ... asked for another follow-up examination of differential blood count in Subject No. 13 in light of a neutrophil count of 29.6% at follow-up in that subject. The study site will take care of this. That control examination shall be scheduled at approximately two weeks after the subject's regular follow-up examination.</p> <p>DMC Chairman Prof. ... asked for an elementary statistical evaluation of FEV1 (in % of predicted) at predose and all post-dose time points as a table or line diagram (mean ± error bars) for each dose group as it seemed that FEV1 tended to decrease a little at +0.5 h post dose.</p>	<input checked="" type="checkbox"/>	Will the study be continued as planned acc. to protocol? What is the next dose level to be administered in the next dose group? 120 mg ... in 4 ml solution or matching placebo	<input type="checkbox"/>	Will the study be prematurely terminated?	<input type="checkbox"/>	Will the study be modified, e.g., will an interim dose level be investigated in the next cohort? If yes, specify:
<input checked="" type="checkbox"/>	Will the study be continued as planned acc. to protocol? What is the next dose level to be administered in the next dose group? 120 mg ... in 4 ml solution or matching placebo						
<input type="checkbox"/>	Will the study be prematurely terminated?						
<input type="checkbox"/>	Will the study be modified, e.g., will an interim dose level be investigated in the next cohort? If yes, specify:						

Formalization of the process of interim data review

The process of interim data review can be formalized in different ways:

DSMB – Drug Safety Monitoring Board

- Consists of independent external experts
- Functions and responsibilities are described in DSMB Charter
- Usually own biostatistician
- Committee members are commonly unblinded on a regular basis (e.g., oncology trials)
- This is a fully independent committee with extensive powers

DMC – Data Monitoring Committee

- Consists of independent external experts
- Functions and responsibilities are described in DMC Charter

Expert Committee consisting of experts of the sponsor and study site/CRO

- Involvement of external experts who are members of the trial team (e.g. pharmacokineticist) only if needed
 - Less formalized process, details usually described in clinical trial protocol
 - Nevertheless, every Dose Escalation Meeting and decision must be documented
-



Arbeitsgemeinschaft
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DSMB / DMC Charter

Defines

- Composition of the DSMB / DMC
- Meeting rules
- Selection of key safety data to be completely reviewed
- Format of data presentation
- Rules for additional *ad-hoc* summary statistics of certain parameters of interest
- Competencies and powers of the DSMB / DMC
- Criteria for unblinding (full / partial)
- Stopping criteria for study termination
- Voting rules
- Documentation

Special requirements for special first-in-human trials

- Maintenance of specific emergency medication (e.g., antidote, causal therapy taking into account the mechanism of action)
- Availability of special instrumental methods for measuring specific safety or PD parameters (e.g., long-term pulse oxymetry, impedance cardiography, telemetry)
- If necessary, availability of clinical specialists who are experienced in the implementation of special instrumental procedures, or if this is requested for safety reasons
- Special case:
Conduct of the first-in-human trial in a clinic, when the trial is to be conducted in patients because the trial conduct in healthy subjects would not be justified (oncology)

Some conclusions

- The clinical conduct of a first-in-human trial is subject to special requirements for spatial, technical and personnel equipment.
- These demands arise from safety considerations and certain peculiarities in the procedures of first-in-human trials.
- Some special requirements are described in the current regulations and in new guidelines and recommendations.
- Some aspects are currently being discussed (e.g., umbrella protocols).
- Some requirements are not formulated in detail, but inevitably result from the obligation to exercise due medical care.
- In practice, a certain standard has been established for phase I units, which is also requested by ethics committees and supervisory authorities.