Approach to the Critique of High Risk Clinical Trials

Disclaimer: The information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
Fundamental Element

**Good Clinical Practice** (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
THE PRINCIPLES OF ICH GCP
E6: 13 elements

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 requirements.

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.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
ICH GCP: E6: 13 elements

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

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10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
EMEA guidance: FIH CTs with IMPs
Strategies to identify and mitigate risks

**Considers**
- Quality
- Non-clinical
- Clinical testing strategies and designs

FIH guidance (like most) is not stand alone

**Should be considered with:**
- Non clinical guidance on
  - Quality of pharmaceuticals - M3
  - Preclinical safety of biotechnology derived products - S6
  - QT interval prolongation - S7B
  - Safety pharmacology – S7A
  - Toxicokinetics – S3A
- Clinical aspects
  - GCP – E6
  - general considerations – E8
  - Monitoring and Pharmacovigilance

*Does not apply to Gene and Cell therapies*
FIH CTs as in all CTs
Safety is Paramount

- Experimental approaches should be science based
- Justified on a CASE-BY-CASE basis
- Ability of non-clinical testing may be limited
- Dose determination is key both, initial and subsequent escalations and intervals between doses
- Defining a development program is an iterative process integrating safety needs from many sources - includes the regulator

Quality

- Attributes should not be a source of risk!
- Should be considered in a risk assessment preceding FIH trials
- Non-clinical studies should be representative of the material for FIH
Non-clinical Aspects

- Demonstration of relevance of animal model
- Pharmacodynamics
- Pharmacokinetics
- Safety pharmacology
- Toxicology
- Estimation of first dose
  - NOAEL - No Observed Adverse Effect Level
  - MABEL - Minimum Anticipated Biological Effect Level

Identifying Factors of Risk

- Mode of Action
- Nature of the target
- Relevance of the animal models
- All case-by case
Mode of Action

- Novelty / extent of knowledge of supposed mode of action
- Nature and intensity; extent, amplification, duration, reversibility
- Dose response linear or non-linear?
- Connected to multiple signal pathways?
- Biological Cascade or cytokine release
  - eg. immune system, blood coagulation system
- Related to compound with similar modes of action
- Are there animal models?
  - Transgenic, knock-in or knock-out animals
  - Enhanced receptor interaction

Nature of Target

- Structure
- Tissue distribution (including expression in/on human immune cells)
- Cell and disease specificity, regulation
- Polymorphisms of target in relevant animal species
- Does the relevant animal model take into account the following comparisons to humans;
  - Target
  - Structural homology
  - Distribution
  - Signal transduction pathway
  - If model is questionable should be considered by the sponsor!
**Drug Product, Type or Class**

- Route of administration: oral, intravenous, intramuscular, subcutaneous, inhalation, intranasal, topical (local or systemic)
- Pharmaceutical, biologic, radiopharmaceutical: is it a novel class of drug substance/product? (e.g., nanosuspension, oligonucleotide, gene therapy)
- Potential risks with drug product or class, such as:
  - immunogenicity (e.g., PRCA)
  - hypersensitivity
  - human-sourced excipients (e.g., risk of BSE, viruses, etc.)
  - immunosuppression
  - birth defects
  - QT-prolongation
  - drug-dependence
  - liver toxicity
  - other…

**Disease Target**

- Morbidity and mortality of the disease
- Prevalence of the disease
- Availability of current therapies
- Current clinical practice guidelines
- Potential for exaggerated pharmacodynamic effects
**Subject Population**

- Healthy adults
- Adult patients
- Elderly patients
- Pregnant women
- Paediatric
- Vulnerable patients
- *Pharmacogenomic considerations*

**Clinical Aspects**

- **General**
  - Design to mitigate risk; study population, trial sites, route and rate of administration, # per dose (cohort size), sequence and interval between dosing within a cohort, dose escalation increments and transition, stopping rules,
  - Rapid access to treatment allocation of codes (for placebo if applicable)
- **Choice of subjects**
  - Should be fully justified on case-by-case
  - Is risk quantified and justified and include short and long term toxicity?
  - Is the lack of relevant animal model addressed?
  - Have the potential pharmacogenomics differences between a targeted patient group and health volunteers been considered?
  - Could the trial interfere with the patients potential ability to benefit from other products, interventions or trials?
  - Are the subjects involved or recently involved in another CT?
Health Products and Food Branch

Protocol Design

- Route and rate of IV infusion
- Precautions between doses in the same cohort
- Precautions to apply between cohorts
- Dose escalations scheme
- Stopping rules
- Monitoring and communication of ADRs
  - expedited reporting of SUSARS to National Competent Authority (regulator), REB and Investigators
- Facilities and personnel
  - Adequate and appropriately trained
  - Immediate access to resuscitation and stabilizing equipment for;
    - Cardiac emergencies
    - Anaphylaxis
    - Convulsions
    - Hypotension
    - Cytokine release syndrome
- Ready availability to an ICU
- Adequate rationale for more than a single site

Health Products and Food Branch

Strategies for mitigating risk

- Calculation of initial dose
- Subsequent dose escalations
- Conduct of the CT
Scanning the Application

- To determine the amount of risk and if there could be major gaps – As a manager or Chief – who do you assign this review to???

- This helps in prioritization, obtaining information and mobilizing expertise for decision-making:
  - Stage of development / phase of trial?
  - Disease target?
  - Subject population?
  - Potential safety concern(s) in drug class?
  - Sponsor?

Who is the Sponsor?

- Large pharmaceutical company
- Small pharmaceutical or biotech
- Domestic or foreign
- Academic
- Disease cooperative or group

Protection of clinical trial participants always prevails
Informed Consent
Section 4.8 of ICH E6

The ICH definition:

Process by which a subject voluntarily confirms their willingness to participate in a particular trial after having been informed of all aspects of the trial that are relevant to a subject's decision to participate. It is documented by means of a written signed and dated ICF.

20 Elements (a) – (t) of the ICF according to GCP

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.
(b) The purpose of the trial.
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
(e) The subject's responsibilities.
20 Elements (a) – (t) of the ICF according to GCP

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
20 Elements (a) – (t) of the ICF according to GCP

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The **foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated**.

(s) The **expected duration** of the subject's participation in the trial.

(t) The **approximate number of subjects** involved in the trial.

Can Risk Benefit Concerns be Mitigated Through the ICD?

- More clearly state availability of alternative treatment
- More clearly identify risks, including all procedures
- Clearly identify voluntary aspect of both enrolment and continuation
- Ensure benefits are not overstated
- Language is appropriate
  - easily understood by subjects