



The University of Hong Kong



Hospital Authority

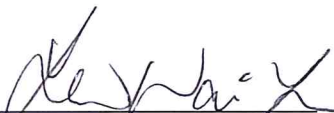
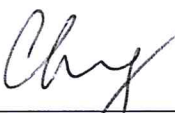
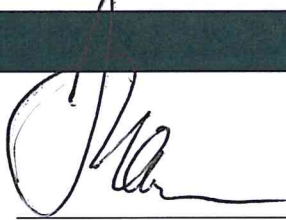


The Chinese University
of Hong Kong

Consortium on Harmonization of Institutional Requirements for Clinical Research (CHAIR)

Guideline on Ethics Oversight and Scientific Evaluation of Phase 1 Clinical Trials

Document Particulars	
Document Type	<input type="checkbox"/> SOP ^(a) <input checked="" type="checkbox"/> Guideline ^(b) <input type="checkbox"/> Working Manual ^(c)
Document Reference No.	CHAIR/GL/001
Initial Issue Date	1st April, 2014
Version No.	2
Issue Date	9th July, 2018
Effective Date	16th July, 2018

Approval		
		
Professor W L LAW Acting Dean, Li Ka Shing Faculty of Medicine The University of Hong Kong	Dr K L CHUNG Director (Quality & Safety) Hospital Authority	Professor Francis K L CHAN Dean, Faculty of Medicine The Chinese University of Hong Kong
Date: 25 June 2018	Date: 5 July 2018	Date: 28 JUN 2018

- (a) A Standard Operating Procedure (SOP) is an official document outlining the necessary procedures for executing a specified task, which shall be approved by the authorized representative(s) of the organization(s) and complied with by the relevant operating unit(s) and personnel.
- (b) A Guideline is a guidance document for elaborating and facilitating compliance with the relevant SOP(s) or requirement(s), which could be approved by the authorized quality assurance specialist(s) and/or the authorized representative(s) of the organization(s).
- (c) A Working Manual is a document providing more details about execution of the required procedures under the relevant SOP(s), which could be approved by the authorized representative(s) of the operating unit(s) responsible for the task concerned and followed by the relevant operational personnel.

Version and Review History

[illegible]

Table of Contents

1.	Background and Scope	4
1.1	Background	4
1.2	Scope	4
2.	Characteristics of Phase 1 Clinical Trials	5
2.1	Definition of Phase 1 Clinical Trials	5
2.2	First-in-Human Clinical Trials	6
2.3	Subsequent Phase 1 Clinical Trials	7
3.	Ethics Oversight	7
3.1	Ethics Oversight by Special Panels for Phase 1 Clinical Trials	7
3.2	Subject Selection	8
3.3	Subject Recruitment	9
3.4	Informed Consent	10
3.5	Expertise and Experience of Investigators and Study Site Personnel	12
3.6	Study Site Facilities	12
3.7	Ongoing Safety Monitoring and Reporting	13
3.8	Medical Emergency	13
4.	Scientific Evaluation	14
4.1	Scientific Evaluation by Joint Scientific Committee	14
4.2	Risk Assessment for Investigational Medicinal Products	15
4.3	Scientific Basis of Subject Selection	16
4.4	Formulation and Route of Administration	16
4.5	Starting Dose	17
4.6	Dose Escalation	17
4.7	Dosing Schedule	18
4.8	Stopping Rules	18
	Appendix 1: List of Abbreviations	20
	Appendix 2: References	21

1. Background and Scope

1.1 Background

- 1.1.1 The development of new and better medicines is crucial for human healthcare. Clinical trials represent the final and essential step in new drug development – bringing potential new medicines from laboratories to the bedside – and are of great value to patients, medical practitioners, medical institutions and the society at large.
- 1.1.2 Clinical trials on new drugs are commonly classified into four phases. Phase 1 is the first stage of human testing aiming at assessing human pharmacology and safety. Phase 2 focuses on therapeutic exploration in patients with the target disease. Phase 3 aims at confirmation of efficacy and safety through testing of a drug in a statistically sufficient number of patients in randomized controlled trials. Phase 4 involves continuing assessment of safety and/or efficacy of a drug in real clinical environment after marketing authorization.¹
- 1.1.3 The rights, safety and well-being of trial subjects are always the paramount considerations in clinical trials.^{2,3} These are of even higher importance in phase 1 clinical trials because their planning and management could only be based on pre-clinical data and very limited human data (if any), and the subjects are normally not anticipated to enjoy direct medical benefits.
- 1.1.4 The University of Hong Kong (“HKU”), The Chinese University of Hong Kong (“CUHK”) and the Hospital Authority (“HA”) have for long been in close collaboration in medical research, education and services in Hong Kong. They are committed to supporting and upholding the standard of clinical trials with the ultimate aims of advancing healthcare technologies and services and improving the health and quality of life of people in Hong Kong. In order to facilitate phase 1 clinical trials in Hong Kong whilst safeguarding the rights, safety and well-being of trial subjects, the three institutions jointly developed this guideline to provide guidance on ethics oversight and scientific evaluation for phase 1 clinical trials. This guideline also serves as a good reference for investigators, study coordinators and other management and operational personnel involved in phase 1 clinical trials.

1.2 Scope

- 1.2.1 This guideline is intended as a guidance for ethics oversight and scientific evaluation of phase 1 clinical trials on novel chemical or biological drugs not registered in Hong Kong – hereinafter referred to as investigational medicinal products (“IMPs”) –

undertaken by and/or conducted in the premises owned, managed and/or controlled by HKU, CUHK and/or HA.

- 1.2.2 The definition of phase 1 clinical trials, for the purpose of ethics oversight and scientific evaluation based on this guideline, is set out in Section 2.1.

2. Characteristics of Phase 1 Clinical Trials

2.1 Definition of Phase 1 Clinical Trials

- 2.1.1 Phase 1 is the first stage of testing of an IMP in humans, including initial clinical trials aiming mainly at evaluating the IMP's:^{1,5}

- (a) safety profile;
- (b) toxicity;
- (c) pharmacokinetics (“PK”); and/or
- (d) pharmacodynamics (“PD”).

- 2.1.2 Phase 1 clinical trials are exploratory in nature and may be conducted in patients or healthy volunteers, where direct therapeutic benefit on trial subjects is usually not expected.^{4,5}

- 2.1.3 For the purpose of this guideline, a phase 1 clinical trial means a clinical trial on an IMP and fulfills any of the following criteria:

- (a) A clinical trial which is designated a phase 1 clinical trial on its protocol;
- (b) A clinical trial on an IMP which is tested in humans for the first time;
- (c) A clinical trial with only human pharmacology (such as PK and PD), toxicity and/or safety (but not efficacy) of an IMP as its primary objective(s);
- (d) A clinical trial which is reasonably deemed by the relevant institutional review board/research ethics committee (“IRB/REC”) a phase 1 clinical trial or equivalent to a phase 1 clinical trial from the perspective of clinical risk.

- 2.1.4 For the avoidance of doubt,

- (a) any PK, PD, bioavailability (“BA”) or bioequivalence (“BE”) trial on a chemical drug (i) with its active chemical entity registered in Hong Kong or any country/place in the “ICH Region”; and (ii) with the same route of administration of the corresponding chemical drug registered in Hong Kong or any country/place in the “ICH Region”; shall not be regarded as a phase 1 trial under this guideline; and

- (b) any clinical trial on a biosimilar that is not registered in Hong Kong and fulfills the criteria under Section 2.1.3 shall be regarded as a phase 1 trial under this guideline;

where the “**ICH Region**” refers to the corresponding countries/regions of the ICH’s founding regulatory members, standing regulatory members and regulatory members (currently including the European Union, United States, Japan, Canada, Switzerland, Brazil, China and Korea).

2.2 First-in-Human Clinical Trials

- 2.2.1 A first-in-human (“**FIH**”) trial is a clinical trial where an IMP is tested in humans for the first time.
- 2.2.2 A FIH trial is usually a single ascending dose (“**SAD**”) trial, where a single dose of an IMP (or matching placebo, if applicable) is given to each subject in a cohort of a small number of subjects (usually three to eight), and the dosage increases (within each cohort or from cohort to cohort) until the maximum dose defined in the protocol is attained or intolerable toxicity is observed and the maximum tolerated dose (“**MTD**”) is identified. SAD trials are usually in parallel group design or crossover design.^{5,6}
- 2.2.3 In parallel group design, the subjects in each cohort are only given one dose of the IMP (or matching placebo, if applicable), and the dosage increases sequentially from cohort to cohort. The parallel group design is a traditional design which avoids exposing subjects to multiple doses of an IMP, and is especially suitable for IMPs with long half-lives or biological IMPs. It however requires much more subjects than in crossover design.⁶
- 2.2.4 In crossover design, each subject in a cohort receives increasing single doses of the IMP (or matching placebo, if applicable) in regular intervals. The crossover design has the advantages of efficient use of subjects (i.e. evaluation of each subject in multiple doses) and allowing subjects to serve as their own controls. However, it is not suitable for IMPs with long half-lives or biological IMPs. Crossover design could be practiced by using sequential cohorts (where a cohort receives sequential increasing doses before dosing starts in another cohort) or interlocking cohorts (where cohorts receive escalating doses in turns).⁶

2.3 Subsequent Phase 1 Clinical Trials

2.3.1 Following a FIH SAD trial, an IMP is usually evaluated further in a multiple ascending doses (“**MAD**”) trial where each subject in a cohort receives multiple doses of the IMP at the same dosage, and the dosage increases from cohort to cohort until a predefined dose level is reached or intolerable toxicity is observed.⁵

2.3.2 Other phase 1 trials may include:

- (a) influencing factor trials, where the effects of potentially influencing factors (e.g. age, gender, genetic) on IMPs’ activities are assessed;
- (b) food-drug interaction trials, where the effects of certain types of food on the PK and PD properties of IMPs are assessed;
- (c) drug-drug interaction trials, where the influences on the effects of IMPs by concomitant drugs are assessed;
- (d) cardiac safety trials, where IMPs’ effects on the QT interval of subjects are assessed;
- (e) PK/PD trials in patients with impaired hepatic or renal function, where the PK/PD properties of IMPs are assessed in patients with impaired hepatic or renal function; and
- (f) BE trials on biosimilars, where the bioequivalence of biosimilars with their respective referenced biological medicinal products are evaluated.

3. Ethics Oversight

3.1 Ethics Oversight by Special Panels for Phase 1 Clinical Trials

3.1.1 The rights, safety and well-being of trial subjects are the most important considerations in clinical trials. The relevant IRB/RECs overseeing clinical research conducted under HKU, CUHK and/or HA shall have the responsibility of performing continuous ethics oversight over phase 1 clinical trials through their respective Phase 1 Clinical Trials Review Panels (“**Phase 1 Panels**”).

3.1.2 A Phase 1 Panel shall have its membership composition specified in its IRB/REC’s standard operating procedures (“**SOPs**”) and shall consist of a minimum of five members including:

- (a) at least one member whose primary expertise or area of interest is in medical, clinical or biological sciences or related disciplines;
- (b) at least one member whose primary expertise or areas of interest is not in medical,

- clinical or biological sciences or related disciplines; and
 - (c) at least one member who is neither directly affiliated with the study site nor the direct family member of any person affiliated with the study site (irrespective of the member's primary expertise or area of interest).
- 3.1.3 The scope of ethics oversight specific to phase 1 trials, among other general considerations in clinical research ethics, may include:
- (a) subject selection;
 - (b) subject recruitment;
 - (c) informed consent;
 - (d) expertise and experience of investigators and study site personnel;
 - (e) study site facilities;
 - (f) ongoing safety monitoring and reporting; and
 - (g) medical emergency.

3.2 Subject Selection

- 3.2.1 The primary objective of clinical trials is to answer research questions rather than medical treatment or clinical care. Only the population that supports achievement of the scientific objectives and answering the research questions of a clinical trial should be included in the trial (see Section 4.3).⁴
- 3.2.2 Since phase 1 trials aim mainly at evaluating the safety, toxicity, PK and/or PD of IMPs and protection of subjects' safety is of paramount importance, trial subjects involved in phase 1 trials are usually healthy adults or adult patients with the targeted diseases of the IMPs.^{6,7}
- 3.2.3 Some special populations, such as elderly, children, pregnant women and patients with impaired hepatic or renal function, are of possibly higher clinical risk, and therefore sufficient justifications and suitable precautions shall be available in order to include them in phase 1 trials. As a general rule, such special populations should not be involved unless the IMP concerned is intended for use in them, and it is reasonably believed that trial results from general adult subjects may not reflect the effects in such special populations.^{5,7}
- 3.2.4 Special ethical considerations shall be taken in recruiting vulnerable subjects. Vulnerable subjects are individuals whose willingness to participate in clinical trials may relatively easily be unduly influenced by biases or coercive factors, or who are incapable of giving free informed consent through a usual informed consent process.²

Examples of vulnerable subjects include impoverished persons, ethnic minority groups, prisoners, patients in emergency conditions, illiterates, mentally incapacitated persons, children, and subordinates or students of investigators.⁵ If such vulnerable subjects are to be included in a phase 1 trial, their vulnerability shall be expressly addressed to the relevant IRB/REC and proper arrangements shall be made in the informed consent process to ensure that the subjects can give voluntary informed consent free from any undue influence.

3.3 Subject Recruitment

3.3.1 In recruitment of subjects, the following three fundamental ethical principles set out in the Belmont Report (i.e. the report entitled “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” which was first drafted by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research at the Belmont Conference Center and officially created by the former U.S. Department of Health, Education, and Welfare in 1979) shall be duly considered:⁸

- (a) Respect for persons, which refers to protecting people’s autonomy of trial participation and allowing for informed consent;
- (b) Beneficence, which refers to maximizing possible benefits while minimizing possible harms to subjects in clinical trials;
- (c) Justice, which refers to fair selection of trial subjects.

3.3.2 Potential subjects for a phase 1 trial may be recruited:

- (a) from the relevant patient pools of the investigators;
- (b) through advertisements or recruitment notices (e.g. posters, leaflets, newspaper advertisements, websites and emails);
- (c) by referral (by other doctors or other people who heard about the trial); and/or
- (d) from the study site’s clinical trial volunteer database containing information of volunteers who provided express consent to be contacted for potential clinical trial opportunities.

3.3.3 All potential subject recruitment methods and the related recruitment materials specific for a trial shall be included in the application to the relevant IRB/REC, and have to be approved by the IRB/REC before being used. For the avoidance of doubt, general advertising and screening of volunteers for registration with a study site’s clinical trial volunteer database do not require approval by an IRB/REC.⁵ A study site should however observe the requirements of and ensure compliance with all

applicable Hong Kong laws and regulations on personal data protection (in particular the Personal Data (Privacy) Ordinance of Hong Kong) in collecting, holding, processing, using, transferring and erasing the personal data of volunteers.⁹

- 3.3.4 Phase 1 trials are usually conducted in cohorts of subjects. Recruitment of subjects over the required number of subjects for a cohort (i.e. as stand-by subjects to replace subjects who provided their informed consent but withdraw before the trial starts) may be practiced if deemed required by the investigator, provided that the arrangement is made clear to and agreed by the subjects in the informed consent process.
- 3.3.5 Overexposure of subjects to IMPs shall be avoided for protecting the safety of subjects. As a general rule, a subject shall not participate in more than one trial at the same time, and shall not participate in another trial in less than three months after completing or withdrawing from the previous trial.^{1,5} The minimum duration required for a subject to participate in the next trial will depend on factors such as the nature of the IMP, overall exposure to the IMP, and the volume of blood taken.⁵
- 3.3.6 Subjects volunteer to take part in a trial are contributing their time, committing to certain lifestyle restrictions, and accepting certain discomfort during the period of the trial. Payment to subjects for their participation in a trial is allowed, provided that the amount shall only be linked to the time spent on the trial, the inconvenience arising from the trial's arrangements and lifestyle restrictions, and the discomfort caused by trial procedures, as well as the trial-related expenses incurred.⁵ For the avoidance of financial coercion, in no circumstances shall payment be made for compensating trial subjects for the risk taken or for providing their biological specimens.

3.4 Informed Consent

- 3.4.1 Since phase 1 trials are usually conducted in cohorts of subjects, briefing of a phase 1 trial to potential subjects is commonly arranged in form of a group introduction which constitutes a part of the informed consent process. Detailed informed consent, however, shall be conducted on an individual basis to avoid group coercion and protect individuals' privacy.
- 3.4.2 The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice ("ICH GCP") sets out 20 essential elements that must be incorporated into the informed consent process for any clinical trial, covering:^{2,10}

- (a) the purposes and arrangements, including:

- the research nature of the trial;
 - the purposes of the trial;
 - the details of the trial treatments and any randomization arrangement;
 - the experimental aspects of the trial;
 - the detailed trial procedures;
 - the expected duration of participation in the trial by each subject;
 - the circumstances where a subject's participation in the trial will be terminated;
 - and
 - the approximate number of subjects involved or to be involved in the trial;
- (b) the potential risks and benefits, including:
- the potential benefits of the study; and
 - the foreseeable risks of the study;
- (c) subjects' rights and responsibilities, including:
- the right of voluntary participation in and free withdrawal from the trial;
 - the availability and details of any alternative treatment;
 - the right to be promptly informed of any new information that may affect subjects' willingness of continuous participation in the trial;
 - the right to contact a designated person for trial-related matters and his/her contact details; and
 - subjects' responsibilities in the trial;
- (d) personal data protection, including:
- the measures to be taken to protect subjects' privacy; and
 - each subject's permission to provide access to his/her personal data by certain designated parties and regulatory authorities;
- (e) compensation and costs, including:
- any payment to subjects;
 - the compensation and treatments available in the event of trial-related injury;
 - and
 - any cost that may need to be borne by subjects.

3.4.3 These 20 elements are also applicable to phase 1 trials. Aspects that are specific to or with higher importance in a phase 1 trial, and need to be emphasized in the informed consent process may include:

- (a) the early explorative nature of the trial;
- (b) the foreseeable risks and uncertainties, considering the lack of or very limited human data on the IMP;
- (c) the possible discomfort arising from trial procedures (e.g. intensive blood-taking);
- (d) the lifestyle restrictions and inconvenience (especially if overnight stay at a study

- site is required);
- (e) the privacy issues (especially if overnight stay at a study site is required);
- (f) the stand-by subject arrangement (if applicable); and
- (g) payment to subjects (if applicable, in particular how payments will be made in case of dropout or premature withdrawal/termination).

3.5 Expertise and Experience of Investigators and Study Site Personnel

- 3.5.1 Each phase 1 clinical trial shall be supervised and finally responsible by a principal investigator appropriately qualified by education, training and experience in clinical trials.^{2,7}
- 3.5.2 The study team for each phase 1 trial shall have qualified medical doctor(s) who are responsible for monitoring the safety of subjects, making medical decisions, and dealing with medical emergencies in the trial.^{2,7}
- 3.5.3 All trial procedures shall be performed by qualified persons, in particular in compliance with the applicable laws and regulations of Hong Kong.⁷ For examples, drugs may be managed by qualified pharmacists, dispensers or pharmacy technicians (as the case may require), and blood specimens may be handled by qualified study coordinators or laboratory technicians (as the case may require). Less experienced personnel shall only perform trial procedures under the supervision of experienced persons. In any case, the final responsibility for the conduct and quality of a trial shall always stay with the principal investigator.

3.6 Study Site Facilities

- 3.6.1 All phase 1 trials shall be conducted in appropriately located and equipped study sites.
- 3.6.2 A study site for a phase 1 trial shall, corresponding to the trial's degree of risk, be:⁷
 - (a) located in a convenient location in a hospital that allows quick medical emergency support by the hospital's resuscitation team and rapid transfer to the hospital's Intensive Care Unit ("ICU") if needed; and
 - (b) equipped with equipment and facilities required for proper and safe conduct of the trial.
- 3.6.3 If overnight stay at a study site is required, the study site should be equipped with beds and other living amenities and services such as:⁷
 - (a) bathrooms and toilets, with emergency call buttons and un-lockable from outside

- in case of emergencies and allow access control by study site personnel;
- (b) leisure area, with facilities such as television, computers and internet access;
- (c) dining area and catering service; and
- (d) laundry service.

3.7 Ongoing Safety Monitoring and Reporting

- 3.7.1 The risk factors and possible adverse reactions of an IMP shall be identified based on available information such as the nature of the IMP, pre-clinical data and available human data (see Section 4.2). A comprehensive safety monitoring plan shall be developed and made available to study site personnel for identifying and managing those foreseeable adverse reactions and other unanticipated adverse events.⁴
- 3.7.2 While staying at the study site, all the subjects shall be carefully supervised by study site personnel for safety monitoring. If deemed required based on risk assessment, continuous monitoring of subjects by telemetric/physiological monitoring systems should be arranged.
- 3.7.3 Serious adverse events (“SAEs”) observed from the subjects at the study site shall be reported to :
 - (a) the relevant IRB/REC within 48 hours of awareness of the event by the study team (or earlier if so required by the relevant IRB/REC’s SOP);
 - (b) the sponsor according to the requirements of the protocol and the sponsor (for sponsored clinical trials); and
 - (c) the local regulatory authority according to the laws and regulations of Hong Kong.

3.8 Medical Emergency

- 3.8.1 A medical emergency mechanism shall be established at a study site to deal with any medical emergency situation in phase 1 trials.^{5,7}
- 3.8.2 For a FIH trial, the hospital’s department(s)/unit(s) providing resuscitation shall be notified before initiation of the trial and be informed of the necessary information about the trial (e.g. trial initiation day, trial duration, anticipated number of subjects, nature of the IMP and any special precaution).
- 3.8.3 At least one study team member trained on basic life support (“BLS”) and holds a valid BLS certificate shall be on duty during the period of trial participation by the subjects at the study site. For a FIH trial, an investigator shall be on-site at the first

few hours (usually about five hours) of IMP dosing for the purpose of intensive safety monitoring and immediate resuscitation if needed. On-site support by a critical care specialist or anesthetist may also be arranged if deemed required on the basis of clinical risk assessment.

- 3.8.4 In case of a critical adverse event observed at the study site, study site personnel shall immediately call the hospital's resuscitation team. Before the resuscitation team arrives, the critical care specialist, anesthetist or the BLS certificate holder on duty (as the case may be) may perform basic on-site resuscitation to help stabilize the subject's condition.
- 3.8.5 Upon receipt of an emergency call, the hospital's resuscitation team will immediately go to the study site and perform resuscitation procedures according to the established hospital practice.
- 3.8.6 Once the subject is stabilized, he/she may first be admitted to the hospital's ICU for immediate treatment and, on the ICU's professional judgment, be subsequently transferred to a relevant clinical department for further treatment and clinical management.

4. Scientific Evaluation

4.1 Scientific Evaluation by Joint Scientific Committee

- 4.1.1 Scientific evaluation shall be performed, upon request by a relevant IRB/REC and prior to initiation of a phase 1 clinical trial, by a Scientific Review Panel ("**SRP**") under a Joint Scientific Committee ("**JSC**") established jointly by HKU, CUHK and HA for the purposes of protecting the safety of trial subjects and ensuring the scientific validity of the phase 1 trial.⁷
- 4.1.2 The SRP shall comprise expert members with the relevant scientific expertise, such as clinical sciences, pharmacology/clinical pharmacology, pharmacy and medical statistics, according to the JSC's SOPs.
- 4.1.3 The scope of scientific evaluation may include:
 - (a) IMP risk assessment;
 - (b) scientific basis of subject selection;
 - (c) formulation and route of administration;
 - (d) starting dose (for FIH trials);
 - (e) dose escalation (for ascending dose trials);

- (f) dosing schedule; and
- (g) stopping rules.

4.2 Risk Assessment for Investigational Medicinal Products

- 4.2.1 Identifying the risk factors of an IMP is of the utmost importance to protection of subjects' safety. According to the European Medicines Agency's Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products (EMA/CHMP/SWP/28367/07 Rev. 1), special considerations may be made on:⁴
- (a) the mode of action of an IMP;
 - (b) the nature of an IMP's target; and
 - (c) the relevance of the animal models used in pre-clinical testing of an IMP.
- 4.2.2 An IMP's anticipated mode of action, including the nature and intensity of the IMP's effect on the target and other non-targets (e.g. mechanism, extent, duration and reversibility of action), will be evaluated where relevant, and special attention will be put on each mode of action that:⁴
- (a) is novel and the knowledge on which is relatively limited;
 - (b) involves a target connecting to multiple signaling pathways (e.g. pleiotropic effects);
 - (c) involves targets that can be ubiquitously expressed (e.g. immune responses); or
 - (d) may lead to amplification of an effect (e.g. through a biological cascade).
- 4.2.3 The nature of an IMP's target in humans could be a risk factor. Details of the target's nature, such as its structure, distribution, cell specificity, biological function, biological regulation, level of expression and population variation, will need to be carefully evaluated where relevant. A target without a good extent of knowledge on its nature is deemed an additional risk.⁴
- 4.2.4 Risk assessment of an IMP in a phase 1 trial (especially FIH trial) is based mainly on pre-clinical animal data (e.g. data about PK, PD, toxicology and the target in animal species). The predictive power of such animal data for safety in humans depends on the relevance of the animal models. Use of animal models with uncertain relevance is deemed an additional risk.⁴

4.3 Scientific Basis of Subject Selection

- 4.3.1 Subjects participating in phase 1 trials, whether patients or healthy volunteers, are normally not expected to have any direct therapeutic benefit, and protection of subjects' rights, safety and well-being are of the utmost importance. Only suitable study population should be selected, where the risk to the subjects could be justified, to allow answering of the trial's research questions.⁴
- 4.3.2 Major factors that need to be considered in selecting subject populations for a phase 1 trial may include:^{4,6}
- (a) the relative risks of the IMP in different subject populations and the populations' tolerability to potential adverse effects;
 - (b) the IMP's target and the presence of the target in the subject populations;
 - (c) pharmacogenomic difference between the subject populations;
 - (d) variability of subjects within each population; and
 - (e) the potential benefits of the trial (if any) to different subject populations.

4.4 Formulation and Route of Administration

- 4.4.1 The formulations of IMPs normally have not been optimized during phase 1 trials (especially FIH trials), and therefore specific preparation of IMPs rather than simply direct dispensing (e.g. reconstitution for intravenous infusion, preparation of oral solution or suspension, capsule-filling) at the study site's pharmacy may be required. The study site shall have the appropriate facilities and qualified persons for performing the required preparation and management of the IMPs.⁶
- 4.4.2 The formulation and route of administration of an IMP shall be determined based on pre-clinical and/or previous clinical data (if any), especially data about absorption, distribution, metabolism and excretion ("ADME"), as well as the need for flexibility for dose adjustments on site.⁶
- 4.4.3 Intravenous administration is the most flexible for dose adjustment. If an IMP is to be administered intravenously, a slow infusion (probably over hours) is preferred over a rapid injection unless otherwise justified, as this will help mitigate acute adverse reaction. For the convenience of dose adjustment, oral formulations are normally supplied in the form of oral powder – which is usually prepared as an oral solution or suspension or filled into capsules for administration. If tablet formulations are used, different dose strengths should be readily available to allow flexible dose adjustments through combinations of different dose strengths.⁶

4.5 Starting Dose

- 4.5.1 In FIH trials, determination of the first IMP dose is of great importance to risk management and protection of subjects' safety. There are two common methods for estimation of starting IMP dose, including:⁵
- (a) estimation based on the no observed adverse effect level ("NOAEL"), as recommended by the U.S. Food and Drug Administration ("U.S. FDA");¹¹ and
 - (b) estimation based on the minimal anticipated biological effect level ("MABEL"), as recommended by the European Medicines Agency ("EMA").⁴
- 4.5.2 NOAEL is the highest dose of an IMP tested in an animal species in pre-clinical toxicology studies, at which no significant increase in the frequency and/or severity of any adverse effect is observed. NOAEL shall be converted to a human equivalent dose ("HED") based on body surface area. The HED from the most relevant species shall be selected, and then be converted to a maximum recommended starting dose ("MRSD") by applying a safety factor (usually 10-fold or above). This method takes reference to the IMP dose rather than exposure, and aims at identifying a maximum dose with reasonably acceptable toxicity rather than a dose with minimal pharmacological activity in humans.¹¹
- 4.5.3 MABEL is the lowest IMP dose that exerts a minimal biological effect in humans. Calculation of MABEL requires the use of all relevant data from animal and human cells in vitro (e.g. target binding and occupancy, concentration-response curves), all relevant animal data in vivo (e.g. dose-response curves) and relevant PK/PD modeling, together with the application of a safety factor reflecting risk elements such as the IMP's novelty, potency, mode of action and other uncertainties.⁴
- 4.5.4 If different methods suggest different starting dose, the lowest estimate should be applied unless otherwise justified.⁵

4.6 Dose Escalation

- 4.6.1 Dose finding through dose escalation is an important step in phase 1 clinical trials. In an ascending dose trial, a dose escalation scheme is normally designed taking into consideration the dose-toxicity and dose-response relationships observed in pre-clinical studies and the available data from the previous doses. Generally speaking, if the dose-toxicity or dose-response curves are steeper, the dose increments should be smaller. Bigger dose increments (e.g. three- to five-fold increase) could be allowed at lower dose range (where pharmacological effects may not be observed), whilst

smaller increments should be implemented at higher doses (i.e. at the expected therapeutic range).⁵

- 4.6.2 An experienced medical monitor or a trial-specific data and safety monitoring board (“**DSMB**”) may review the available and relevant data (e.g. vital signs, biochemistry, haematology, adverse events and PK data) and make recommendations on dose escalation (i.e. if the dose should be increased, and if so, whether the dose should be increased according to the original dose escalation scheme or an adjusted scheme).^{12,13}

4.7 Dosing Schedule

- 4.7.1 For the purpose of minimizing the risk exposure of subjects and facilitating quick medical emergency management if needed, a FIH trial usually starts from dosing only one single subject with the IMP (and may be another subject with the matching placebo in parallel). The other subjects in the same cohort are normally dosed sequentially, with an adequate time interval between dosing of two subjects. The duration of the time interval will depend on the IMP’s properties (e.g. toxicity, half-life) and should be justified.^{4,5}
- 4.7.2 Dosing of multiple subjects in the same occasion at short intervals (e.g. 10 minutes) may be practiced for other phase 1 trials, provided that the IMP is not of a high risk (based on risk assessment as outlined in Section 4.2) and appropriate safety monitoring and medical emergency management mechanism are in place (as outlined in Sections 3.7 and 3.8).⁵
- 4.7.3 Dose escalation from one cohort to another cohort should proceed as outlined in Section 4.6. The time intervals between cohorts will depend on the design of the trial (e.g. parallel group, crossover sequential group and crossover interlocking group) and the properties of the IMP.⁴

4.8 Stopping Rules

- 4.8.1 To protect subjects’ safety,
- (a) dosing of an individual subject;
 - (b) dosing of further subjects within a cohort; or
 - (c) dose escalation from one cohort to another cohort;

may be stopped if and when severe adverse event(s) (e.g. clinically significant cardiac abnormalities or changes in organ functions, vital signs, biochemistry or haematology data) are observed.⁶

4.8.2 A trial protocol may, if applicable, specify the detailed stopping rules – on the subject level, cohort level or trial level. Relevant PK and/or PD biomarker assays, if applicable, may be arranged to support rapid evaluation of data and implementation of the stopping rules.⁶

Appendix 1:

List of Abbreviations

ADME	Absorption, distribution, metabolism and excretion
BA	Bioavailability
BE	Bioequivalence
BLS	Basic life support
CHAIR	Consortium on Harmonization of Institutional Requirements for Clinical Research
CUHK	The Chinese University of Hong Kong
DSMB	Data and safety monitoring board
EMA	European Medicines Agency
FIH	First-in-human
HA	Hospital Authority
HED	Human equivalent dose
HKU	The University of Hong Kong
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH GCP	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice
ICU	Intensive care unit
IMP	Investigational medicinal product
IRB/REC	Institutional review board / research ethics committee
JSC	Joint Scientific Committee for Phase 1 Clinical Trials
MABEL	Minimal anticipated biological effect level
MAD	Multiple ascending dose
MRSD	Maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetics
SAD	Single ascending dose
SAE	Serious adverse event
SOP	Standard operating procedure
SRP	Scientific Review Panel
U.S. FDA	United States Food and Drug Administration

Appendix 2:

References

1. General considerations for Clinical Trials, E8, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Jul 1997.
2. Guideline for Good Clinical Practice, E6(R2), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, 9 Nov 2016.
3. Ethical Principles for Medical Research Including Human Subjects, World Medical Association, Oct 2013. (Declaration of Helsinki)
4. Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products, European Medicines Agency, Committee for Medicinal Products for Human Use, 20 Jul 2017. (EMA/CHMP/SWP/28367/07 Rev. 1)
5. Guidelines for Phase 1 Clinical Trials, 2012 Ed, Association of the British Pharmaceutical Industry, 2012.
6. First in Human Studies: Points to Consider in Study Placement, Design and Conduct, Association of the British Pharmaceutical Industry, Jan 2011.
7. Guiding Principles for Management of Phase 1 Clinical Drug Trials (Pilot), State Food and Drug Administration, Dec 2011.
8. Ethical Principles and Guidelines for the Protection of Human Subjects of Research, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Apr 1979. (Belmont Report)
9. Personal Data (Privacy) Ordinance, Chapter 486 of the Laws of Hong Kong.
10. Clinical Research Management and Compliance at Study Sites, 2nd Ed, Hospital Authority Head Office Steering Committee on Research Ethics, Oct 2015.
11. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Jul 2005.
12. NIH Policy for Data and Safety Monitoring, National Institutes of Health, Jun 1998.
13. Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials, National Institutes of Health, Jun 2000.