

First Edition

Malaysian Guideline *for* Phase I Unit Inspection & Accreditation Programme



National Pharmaceutical Regulatory Agency
(NPRA)
Ministry of Health Malaysia



Malaysian Guideline for Phase I Unit Inspection & Accreditation Programme

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This Guideline is adapted from:

1. NCCR 2018, Malaysian Guideline for Good Clinical Practice.
2. NPRA 2014, Malaysian Guideline for Application of Clinical Trial Import Licence (CTIL) and Clinical Trial Exemption (CTX).
3. EMA 2008, Annex V to Procedure For Conducting GCP Inspections requested by the EMEA: Phase I Unit.
4. EMA 2018, Guideline On Strategies To Identify And Mitigate Risks For First-In-Human And Early Clinical Trials With Investigational Medicine Products.
5. MHRA 2015, Phase I Accreditation Scheme Requirements.
6. MHRA 2015, Phase I Accreditation Scheme Guidance Document.
7. CRM 2017, Malaysian Phase 1 Clinical Trial Guideline.

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FOREWORD

A Phase I trial is one of the most important steps in the process of developing a new drug. At this stage of the development, new compounds will be used for the first time in a human being with the primary goal of assessing safety of compounds. Generally, First in Human (FIH) Phase I studies involve considerable risk to volunteers compared to other stages of clinical development.

In line with the National Key Economic Area (NKEA), Entry Point Projects 2 (EPP 2) which focuses on creating a supportive ecosystem to grow clinical research, National Pharmaceutical Regulatory Agency (NPRA) had taken the initiative to review the regulatory framework of FIH studies in Malaysia. Considering the high demand from the industry for FIH studies, NPRA is responsible to ensure the quality system and operation of the Phase 1 unit to mitigate the potential risk in volunteers.

Recognising the importance of safety in a clinical trial, it is paramount that an accreditation program for Phase I units conducting FIH studies is established. This will be the stepping stone to ensure that these units are competent in discharging their duties in the interest of volunteer safety. NPRA has adapted the MHRA Phase I Accreditation Scheme to assimilate international standards into the Malaysian setting. The Drug Control Authority has endorsed this guideline in accordance to the Regulation 29 of the Control of Drugs and Cosmetics Regulation (CDCR) 1984 in the 324 meeting on 31st May 2018.

This guideline should be read together with the Malaysian Guideline for Good Clinical Practice, Malaysian Phase I Clinical Trial Guidelines by Clinical Research Malaysia and other relevant local regulatory requirements.

I would like to thank the committee members for their collective input and spirited effort in making this guideline a reality.



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ABBREVIATION

ALS	Advanced Life Support
BLS	Basic Life Support
CAPA	Corrective Action and Preventive Action
CDCR	Control of Drugs and Cosmetics Regulation
CINP	Centre for Investigational Product
CRO	Contract Research Organisation
CTIL	Clinical Trial Import Licence
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
EMA	European Medicines Agency
FIH	First in Human
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Council of Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
MAD	Multiple Ascending Dose
NCCR	National Committee for Clinical Research
NPRA	National Pharmaceutical Regulatory Agency
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
QA	Quality Assurance
QC	Quality Control
SAD	Single Ascending Dose
SAE	Serious Adverse Events
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reaction

1.0 INTRODUCTION

In line with the Malaysian Economic Transformation Program (ETP) that targets clinical research as one of its main drivers in economic growth, the national regulatory authority has taken the initiative to expand the scope of GCP inspections to encompass Phase 1 Units to create a safe regulatory environment for the conduct for Phase I Clinical Trials in Malaysia. The aims of Phase I unit inspections and accreditation are to ensure that the Phase I unit meets satisfactory standards for avoiding harm to clinical trial subjects and for handling medical emergencies should they arise.

The Phase I Unit inspection is designed to give assurance that units listed on the NPRA Phase I Programme not only meet but surpasses basic requirements under the principles of GCP. This is achieved by having additional “best practice” procedures that embraces the highest standards for avoiding harm to trial subjects and for handling medical emergencies which might occur. This programme will also provide assurance to sponsors that accredited units listed can make significant contributions to enhancing the safety of volunteers and are considered to be centres of excellence for Phase I research.

2.0 REGULATORY FRAMEWORK AND SCOPE

2.1 Regulatory Framework

This guideline should be read in conjunction with Control of Drug and Cosmetic Regulation 1984, The Poison Regulations (Psychotropic Substances) 1989 and Sale of Drug Acts 1952. Under Regulation 29, Control of Drug and Cosmetic Regulation 1984, the Director of Pharmaceutical Services may issue written directives or guidelines to a group of persons as he thinks necessary for the better carrying out of the provisions of these Regulations and in particular relate to clinical trials. This guideline is issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984. First in human clinical trials that involve investigational products shall be conducted at NPRA accredited Phase I units in Malaysia. Under Regulation 30, CDCR 1984, any person who contravenes any directives or guidelines issued by the Director of Pharmaceutical Services commits an offence.

2.2 Scope

This guideline will address any facilities that conduct Phase I clinical trials, in particular for First in Human (FIH) clinical trials in Malaysia. Other Phase 1 clinical trials apart from FIH are not covered under this guideline and may be conducted in any clinical trial site subject to current regulatory requirements. This guideline stipulates that:

1. Phase 1 clinical trials involving FIH shall be conducted at a Phase 1 unit listed under the NPRA accreditation programme.
2. Phase 1 units conducting Phase 1 clinical trials other than FIH are voluntary to be listed under the NPRA accreditation programme.

This guideline will be divided into two main sections:

- Phase I Unit Inspection Application

Administrative procedure for the Phase I Unit which intends to conduct FIH clinical trials and requirements for maintenance of the accredited Phase I unit.

- Phase I Inspection Process

This section delineates the procedures involved in inspections to the Phase I Unit conducted by NPRA. Phase I Unit that complies with the Malaysian Guideline for Good Clinical Practice, Malaysian Guideline for Phase I Unit Inspection and Accreditation Programme and applicable regulatory requirements will be listed into the “National Pharmaceutical Regulatory Agency Phase I Unit Inspection and Accreditation Programme”.

This inspection will verify that all requirements outlined in this guideline, Malaysian Guideline for Good Clinical Practice and applicable regulatory requirements have been met before the Phase I unit will be recommended for listing into the program. The Phase I unit must be able to demonstrate that it is able to carry out clinical trials with compounds at all levels of risk, including those that have never been tested in man and those that require review of risk factors. This means they must have formal procedures in place and appropriately trained and experienced staff available to cover all the requirements stated in **Appendix I**.

3.0 DEFINITIONS

Clinical Trial/ Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial Exemption (CTX)

An exemption issued under regulation 15 (5), Control of Drugs and Cosmetics Regulations 1984 by Director of Pharmaceutical Services which exempts a person who wishes to manufacture product(s) solely for the purpose of producing samples for clinical trials from the provisions of regulation 7 (1) or regulation 18A of Control of Drugs and Cosmetics Regulations 1984.

Clinical Trial Import Licence (CTIL)

A license in Form 4 in the Schedule of the Control of Drugs and Cosmetics Regulations 1984, issued by Director of Pharmaceutical Services under regulation 12(1)(c) of the same Regulations which authorises the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product.

Clinical Trial/ Study Report

A written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Compliance

The state of conformity of a regulated party or a product with a legislative or regulatory requirement or a recognized standard or guideline.

Confidentiality

Prevention of disclosure, to other than authorised individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract Research Organisation (CRO)

A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Drug Control Authority (DCA)

An authority set up under the Control of Drugs and Cosmetics Regulations 1984 and as such its responsibility, role and mandate are defined by law.

Direct Access

Permission to examine, analyse, verify and reproduce any records and report that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Drug

Includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for medicinal purposes.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non - scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory

requirements pertaining to Independent Ethics Committees may differ among countries but should allow the Independent Ethics Committee to act in agreement with GCP as described in Malaysian Guideline for GCP.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Inspector

Any person appointed to be an inspector under Section 3 of Dangerous Drugs Act 1952, Section 31 of Poisons Act 1952, Section 21 of Registration of Pharmacists Act 1951, Section 6A of Medicines (Advertisement and Sale) Act 1956, Section 3 (1) and Section 3 (2) of Sale of Drugs Act 1952.

Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Investigation

Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that non-compliance has occurred and that enforcement measures may be necessary (e.g. product quality complaints, reports from other regulatory authorities, reports of adverse reactions or etc.).

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Medicinal Purpose

Any of the following purposes;

- a. Alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
- b. Diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;

- c. Contraception;
- d. Inducing anaesthesia;
- e. Maintaining, modifying, preventing, restoring or interfering with, the normal operation of a physiological function;
- f. Controlling body weight;
- g. General maintenance or promotion of health or well-being.

Observation

A deviation or deficiency noted by an Inspector during an inspection.

Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

Product

- a. A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose; or
- b. A drug to be used as an ingredient for a preparation for a medicinal purpose.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the Malaysian Guideline for GCP the term protocol refers to protocol and protocol amendments.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

Trial Site

The location(s) where trial-related activities are conducted.

Unregistered Product

Any product which is not registered in Malaysia by the DCA.

4.0 Accreditation Unit Application Procedures

In Malaysia, the NPRA Phase I Unit Accreditation Programme is a voluntary for Phase 1 Units but compulsory for units which is conducting FIH studies. The inspections conducted for the accreditation programme encompass a wider scope than standard GCP inspections and includes a detailed review of the unit's systems and procedures relevant to the accreditation programme's requirements. Any variations to the initial information supplied in the application for certification as listed in the section 6.1 may require a verification inspection to assess the criteria or facilities not previously reviewed.

4.1 Application to the NPRA

The Phase I Unit is required to complete the application form *NPRA Phase I Unit Accreditation Programme Application Form* and submit the application in hardcopy to the NPRA. Application shall be made using the application forms available on the NPRA official website <http://np.ra.moh.gov.my/>. The application shall be signed and dated by a pharmacist employed under the Phase I unit with either of the following qualifications:

- i. Poison Licence Type A for pharmacist in private sector; or
- ii. Annual Retention Certificate holder for pharmacist in the public service.

Responsibility of the applicant

- The applicant is responsible for all the information supplied in support of his/ her application for inspection of Phase I Unit. He/ She shall be responsible for updating any information relevant to the application.
- Any person who knowingly supplies any false or misleading information in connection with his/ her application commits an offence under the Regulation 13(4), CDCR 1984.

4.1.1 Administrative requirements

All Phase I Unit accreditation application including supporting documents should be submitted in a bound form. Binders with durable covers containing A4 sized papers, which can be separated and recombined, are required. External dimensions of the white 2-ring binders should be 290 x 370 mm and 30-50 mm in thickness. Should more than one binder is necessary, binders shall be labelled clearly as with the volume number, as an example "volume 1 of 2", "volume 2 of 2" etc.

Documents should be arranged in the sequence outlined in **Annex I**, and clearly segregated with tab file dividers.

Application form as well as supportive documents shall each be printed on double sided A4 sized paper with one page per sheet. NPRA reserves the right to request the applicant to submit copies of these documents in softcopy.

4.1.2 Language

The application form and all supportive documents must be legible. The application form must be completed in either English or *Bahasa Melayu*.

4.1.3 Documents to be submitted in an application

1	Cover Letter The applicant shall submit a signed cover letter with the application. The cover letter shall be signed by the applicant.
2	Application form A completed <i>NPRA Phase I Unit Accreditation Programme Application Form</i> which can be downloaded from the NPRA official portal shall be submitted. The application shall be signed and dated by the applicant.
3	Phase I Unit Floor map Floor map for all the activities involved in Phase 1 clinical trials
4	Phase I Unit organisation chart a. List of investigator and study personnel b. CV for investigator
5	Standard operating procedures (SOPs) a. Master list of SOPs
6	Management approval letter A letter/agreement from the institution/hospital that agreed to conduct Phase I study in the facility.
7	A list of external service provider Name and address for external service provider for pharmacokinetic analysis, laboratory testing, monitoring, archive, etc.

The application form and supporting documents will be screened and the inspection will be initiated upon complete application.

5.0 INSPECTION OF PHASE I UNIT ACCREDITATION

5.1 Categories of inspection

Description of the inspection categories are as follows:

5.1.1 Provisional Inspection

The purpose of this provisional inspection is to verify that the Phase I Unit has established SOPs and other references in compliance with this guideline, the Malaysia Guideline for Good Clinical Practice, Malaysian regulatory requirements and other established international guidelines before conducting Phase I clinical trial.

The liaison officer will contact the Phase I Unit for the arrangement of provisional inspection upon receiving a complete application.

A registration letter will be issued if the inspection was found to be satisfactory and the Phase I Unit will be listed in the *NPRA Phase I Unit Accreditation Programme* provisionally. The Phase I Unit will be allowed to conduct their first Phase I clinical trial once the provisional registration letter has been received. The provisional registration letter issued will stipulate the need for a full inspection to be conducted on the Phase I Unit within one year. The flow chart for the conduct of a provisional inspection is detailed in Section 5.2

5.1.2 Full inspection

The purpose of this inspection is to verify that the provisionally registered Phase I Unit complies with this guideline, the Malaysian Guideline for Good Clinical Practice, Malaysian regulatory requirements and other established guidelines in order for the Phase I Unit to be officially listed in *NPRA Phase I Unit Accreditation Programme*. The Phase I Unit would undergo a full inspection within **one year** from the date of provisional registration letter as stated under section 5.1.1. The flow chart for the conduct of a full inspection is detailed in Section 5.2

5.1.3 Surveillance inspection

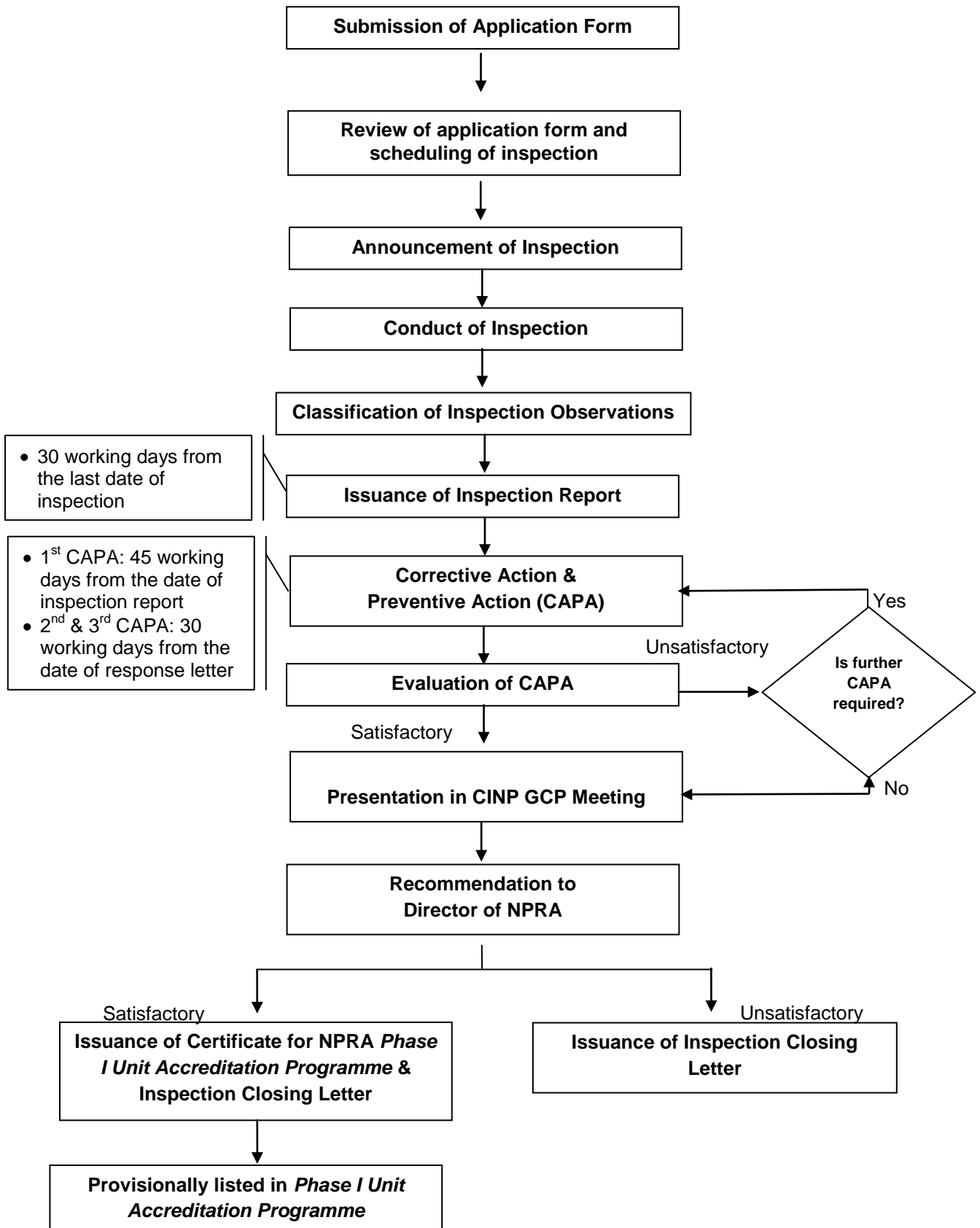
Surveillance inspection is an inspection conducted on the Phase I Unit that had been listed into the accreditation programme to ensure that the Phase I Unit consistently complies with this guideline, the Malaysia Guideline for Good Clinical Practice, Malaysian regulatory requirements and other established guidelines. The accredited Phase 1 unit must have at least one completed Phase 1 study per year. If the Phase 1 Unit intends to continue to be listed in the accreditation programme, the unit shall submit the application form 6 months before the expiry of certificate's validity date. The flow chart for the conduct of a Surveillance Inspection is detailed in Section 5.2

5.1.4 Extraordinary inspection

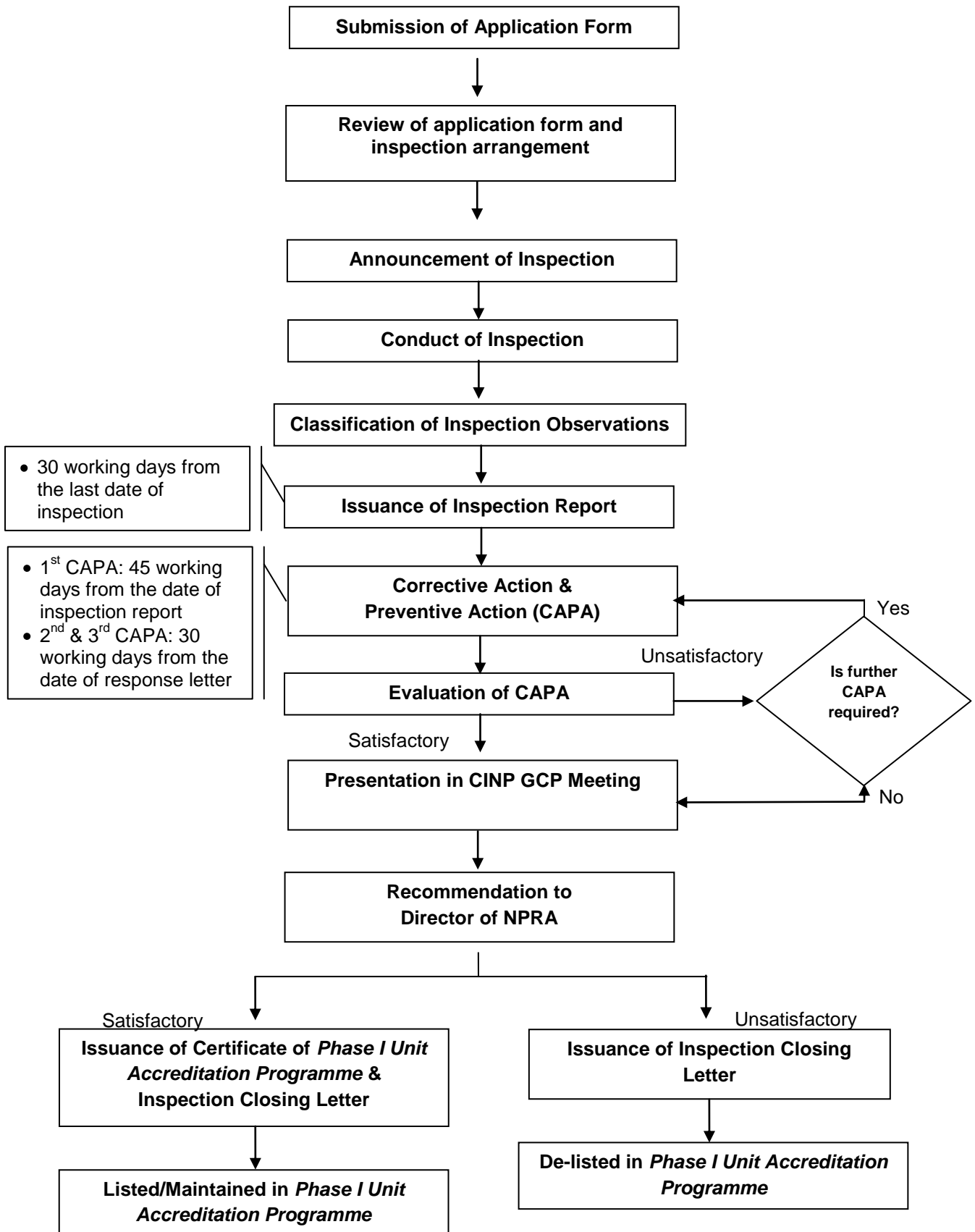
Extraordinary inspection is an inspection that is triggered due to specific concerns. This investigation may be conducted at any time after the Phase I Unit has been listed into *NPRA Phase I Unit Accreditation Programme*. Specific concerns which may trigger an extraordinary inspection are:-

- Complaints received by the regulatory authority on the Phase I Unit.
- Reports received by the regulatory authority on clinical trials with possible ethical and safety issues.
- Non-adherence to legal requirements.
- Verification on the implementation of the corrective actions.
- Other issues deemed necessary by the regulatory authority.

**5.2 Flow Chart: Phase I Unit Inspection
Provisional Inspection**



Full Inspection / Surveillance Inspection / Extraordinary Inspection



5.3 Conduct of Phase I Unit inspection

An inspection shall be conducted based on an established inspection plan whenever possible. The plan shall be based on the type and scope of the inspection.

5.3.1 Announcement

An announcement letter containing the date of inspection, objectives of inspection, duration of inspection, name of inspectors, inspection schedule and pre-inspection documents to be submitted to NPRA shall be issued to the Phase I Unit for all types of inspections. Under normal circumstances, the Phase I Unit shall be required to submit the pre-inspection documents at least two weeks before the agreed inspection date.

5.3.2 Opening meeting

The inspection begins with an opening meeting between the inspectors and representative(s) of the Phase I Unit. It is a requirement that all the key personnel are present at the opening meeting. An attendance will be kept by the inspectors.

The purpose of an opening meeting is to (but not limited to):

- Highlight the scope of the inspection
- Explain the regulatory framework for the conduct of the inspection
- Presentation by the Phase I Unit on the current activities, workload and function of each departments for the conduct of the FIH and Phase I trials.
- Inform the delegation of duties among the inspectors.
- Explain the methods and procedures to be used during the inspection
- Confirm that the resources, documents and facilities needed by the inspector(s) are made available
- Confirm the time and date for the closing meeting and interim meetings, if any.

5.3.3 Conduct of inspection

The inspection activities will be detailed in the inspection agenda. During the inspection, the inspector(s) reserve the right to make adjustments to the plan to ensure all the inspection objectives are achieved. Phase I Unit shall ensure that its management and other key personnel who are familiar with the operations of the unit should be available throughout the conduct of the inspection. The Phase I Unit shall also make available a room for document examination as well as assist in any other inspection related activities.

Inspector(s) shall be granted direct access to all source data/documents, books, records and reports in hardcopy or softcopy that are relevant to the inspection. Direct access is defined as permission to examine, analyse, verify and reproduce any records and reports that are important to the inspection process.

During the inspection, documents as listed in **Appendixes** (but not limited to) may be requested by the inspectors to be inspected. Inspectors will attempt to reconstruct the work process involved in the core activities of the Phase I Unit based on available SOP, documents and records.

For every item, inspector will check, if applicable, how data was generated, collected, reported, analysed or modified.

5.3.4 Closing meeting

At the end of the inspection, a closing meeting shall be held. The main purpose of this meeting is to present the inspection observations to the Phase I Unit management to ensure that the inspection observations are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s). The observations will be presented verbally by inspector(s) during the closing meeting without classification. This is an important time for Phase I Unit management to seek clarification on observations that may have surfaced. Attendance will be kept by the inspector and an acknowledgement will be obtained from the representatives of the Phase I Unit on the evidences collected during the inspection.

5.3.5 Inspection report and CAPA

All observations will be classified as per definitions in *Section 0* and presented as a written inspection report. Inspectors will present all the observations in CINP GCP Meeting for classification before the issuance of inspection report. The Phase I Unit shall receive a written inspection report detailing the observations within 30 working days from the last day of inspection. The Phase I Unit should provide a written Corrective And Preventive Actions (CAPA) in response to the observations within 45 working days for full inspection and 30 working days for surveillance inspection from the date of the inspection report. If the assessed CAPA(s) is/are deemed unsatisfactory, second CAPA may be requested and shall be resubmitted to the inspector no later than 30 working days under normal circumstances.

5.3.6 Final Approval of Inspection Results

5.3.6.1 In Compliance

An Inspection closing letter and a certificate will be issued to the Phase I Unit to indicate that it has been listed under the NPRA Phase I Unit Accreditation Program. Under normal circumstances, the certificate is valid for 3 years. However, depending on the severity of observations in the last inspection, this validity period may be less than the maximum of 3 years. FIH studies are only allowed to be conducted at Phase 1 Units with valid accreditation certificates.

A new certificate shall be issued to replace the registration letter and listed in NPRA Phase I Unit Accreditation Programme. For Phase I Unit already in the NPRA Phase I Unit Accreditation Programme, a renewed certificate shall be issued.

5.3.6.2 Not in compliance

For provisional registered Phase I Unit not in compliance, the facility shall not be listed in the NPRA Phase I Unit Accreditation Programme. For listed Phase I Unit which are not in compliance, DCA may decide to de-list the Phase I Unit from the NPRA Phase I Unit Accreditation Programme.

5.4 Power of Inspector

NPRA Inspector(s) have the right to enter any sites involved in the conduct of Phase I Unit to carry out inspections, take samples, require the production of books and documents, and to take copies of, or copies of entries in, such books and document which inspector(s) reasonably believes would furnish evidence of the inspection and observations without any redaction. Inspectors shall have full access to the facilities and relevant documentations to conduct any type of inspections; otherwise the facility would not be included in the NPRA Phase I Unit Accreditation Programme.

5.5 Classification of findings

The classification of the inspection findings is intended to help classify the severity of observations. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity). The findings shall be classified as critical, major and minor as per the definitions in Sections 5.5.1, 5.5.2, and 5.5.3 respectively.

5.5.1 Critical

Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action required

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents, fraud, manipulation and intentional misrepresentation of data.

5.5.2 Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: data may be rejected and/or legal action required

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

5.5.3 Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

6.0 MAINTENANCE OF PHASE I UNIT ACCREDITATION

6.1 Phase I Unit listed in NPRA Phase I Unit Accreditation Programme

Once the Phase I Unit has been issued a closing letter and compliance certificate, its information will be made available to the public via the NPRA website. The Phase I Unit's name, address, contact person's name, contact number and email address will be available at <http://npra.moh.gov.my> .

Variations to units' accreditation

During the period of accreditation, units will undergo changes, this may be to the personnel, the facilities and the procedures. Where these changes affect either:

- the key personnel (i.e. those listed on the accreditation certificate or providing key support under the terms of the accreditation scheme)
- the facilities (e.g. a change in the location or change of use/design/layout of the unit) or the equipment (e.g. emergency, telemetry, etc.)
- the formalised procedures for key activities described in the accreditation scheme (e.g. over-volunteering, volunteer databases, risk assessment, medical cover/provision, staffing levels, dose escalation etc.)

The unit should assess the changes and whether the NPRA should be notified of these changes, as they may affect their accreditation status and thus need to be reviewed for acceptability. If there is uncertainty the unit should contact the GCP Compliance Section, CINP, NPRA for advice. All decisions and their rationale and/or contact with the NPRA should be documented and retained.

It is acknowledged that many changes will be acceptable based upon office review of the information, however, some may require a short inspection to ensure they are acceptable or may generate some queries and comments from the inspector before being accepted. It is acknowledged that where the changes are urgent (e.g. the addition of a new PI for FIH trials) the unit should contact the GCP Compliance Section to plan the next course of action.

6.2 Removal of a listed Phase I Unit from the programme

The Phase I unit must continue to demonstrate compliance with the requirements in order to maintain their accreditation once accredited. However, should serious issues be identified at the Phase I unit, either by themselves or as a result of information received by NPRA (e.g. through inspection, complaint, serious breach report), this may then lead to a suspension of the unit's accreditation status or removal of accreditation status.

The Phase I Unit may be removed from the NPRA Phase I Unit Accreditation Programme in the event that the facility failed to respond to the observations and final inspection report satisfactorily.

Once the facility is removed from the program, the facility can re-enter into the program by submitting a new application. NPRA will conduct Full Inspection according to existing provisions and procedures.

7.0 APPENDIX I : PHASE 1 UNIT REQUIREMENTS

In addition to there being no unresolved critical and major findings in GCP at the Phase I unit, particular in the area of subject safety (e.g. eligibility, medical cover, subject identification etc.), the following **must** be in place for all Phase I units that wish to be accredited to carry out clinical trials with IP, including those that have never been tested in man (i.e. FIH).

CLINICAL TRIAL DESIGN AND SET-UP

- 1. An agreement with sponsors (or internal memorandum of understanding for in-house units) detailing procedures and responsibilities for notifying the investigator immediately if/when new safety/toxicology data come to light.**

Safety information availability (Appendix 1, point 1)

There should be formal agreements with the sponsor which clearly detail responsibilities for notifying the Principal Investigator (PI) immediately if/when the sponsor becomes aware of new safety/toxicology data. This aspect also needs to be considered in the following circumstances:

- Where the Phase I unit sub-contracts another unit, the agreements should cover onward communication of safety information from the sponsor.
- Where the sponsor is not the owner of the Investigational Product (IP), for example, a non-commercial sponsor for a clinical trial.

When reviewing safety information, the PI should be aware of the quality of the data, for example, that the data contained in the investigator's brochure (IB) is final data and that there is sufficient data for the PI to calculate the starting dose for a first in human (FIH) clinical trial and any dose increments (these calculations may form part of the risk assessment). If the PI requires additional safety information from the sponsor, this should be requested and provided.

- 2. A formal risk assessment and risk management/mitigation strategy. This must be able to demonstrate that the unit (independently of the sponsor) continuously verifies and assesses all aspects of the trial, including any pre-clinical data and pharmacology. For example (but not limited to), trial design, starting dose**

calculations, dose escalation proposals, stopping criteria, exposure, predictable reactions/adverse events, availability of any specific antidotes or emergency treatments and any additional and/or specialist staffing and/or training.

Risk Assessment/Risk Management/Mitigation

Medical emergencies are rare in Phase I trials, however, as many of the products are unregistered the potential risks of the particular IP must be assessed and steps taken to mitigate these risks in accordance with the '*Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products*' (EMA/CHMP/SWP/28367/07) and the Malaysian Guideline for Good Clinical Practice.

Risk assessment is a continuous process throughout the life cycle of the trial. It begins as early as the proposal stage and will potentially change as the study is set-up and recruiting. The risk assessment can influence the development of the protocol, with its drafting and revision based on mitigations to identified risks. It is appreciated that most Phase I units have always performed risk assessments and contingency planning. However, for accreditation this should be a formalised process which is clearly documented. The resultant document, sometimes referred to a risk management plan or a contingency plan (here, the term 'risk assessment' will be used throughout), will be a living document and therefore should be reviewed regularly (e.g. when there are changes to the protocol or unit practices; or at regular intervals depending on the duration of the trial).

It should also be clear what data and documents have been used to perform the risk assessment (for example, the protocol, IB). The version and status of these documents (i.e. draft or final data) should be included as these documents may be updated throughout the course of the trial) and could potentially impact on and require a change to the risk assessment.

The procedure detailing the risk assessment should include the following aspects:

- Who will perform and provide input into the risk assessment.
- How the risk assessment will be documented.
- Who will review and approve the risk assessment.
- Circulation to relevant staff.

- Retention of the risk assessment.
- Maintenance of the risk assessment i.e. continual review and updating it as required.
- Who has responsibility for ensuring compliance with the risk assessment, and for documentation of that compliance.

When performing the risk assessment, units should ensure that all aspects of the trial and the associated risks are considered, that appropriate actions are put in place to mitigate those risks and that both the identified risks and actions are documented. (Note: It is expected that the risk assessment by the unit is done independently of any sponsor assessment and decisions that may already be in the protocol). Aspects that should be reviewed during the risk assessment process include (but are not limited to):

- If it is a FIH trial and if so, confirmation/re-calculation of the starting dose and dose increments.
- Any dose escalation procedures.
- Relevance of study design (i.e. population, administration, assessments etc.)
- IP (i.e. relevance of safety/toxicology information, mode of action, target, pharmacokinetic (PK)/pharmacodynamic (PD) information, etc.)
- Any specific rescue medications/antidotes, supportive emergency facilities and staff, specific emergency scenarios etc.
- Extra staffing/resources (i.e. identifying specific training, expertise, facilities or specific location/wards in unit for conduct of certain trials etc.)

In addition, over the past decade, phase I trials have become much more complex, and a number of objectives that were previously the subject of separate trials are increasingly being integrated into one protocol. A single protocol may now include a single ascending dose (SAD), multiple ascending dose (MAD) and a patient cohort. Therefore, the risk assessment encompassing the FIH aspect of the first cohort of the protocol may be different from the risk assessment for the subsequent cohorts.

See below for some examples of risks and associated mitigation activities:

- Due to the nature of the IP, the risk assessment, protocol or ethics committee condition of approval may require a medical doctor to be on the unit for a specific number of hours post dosing; evidence that this was done should be documented and retained (e.g. in the trial file or as per local practice requirements).
- The risk assessment may identify that as the unit has areas that are not routinely observed (e.g. single bedrooms), the dosing of FIH trials and subsequent post dose monitoring should be in an observed area for a specified time period (e.g. for 24h close observation after dosing in an observed ward). There should be documentation demonstrating that this has occurred.
- The risk assessment may identify a particular medical emergency associated with the class of IP that is not routinely covered by the unit; therefore mitigation may include availability of specific equipment, specific staff training or trial specific emergency scenarios. Again all these actions should be documented as evidence that the risk assessment was followed.

Dose Escalation

It is expected that the Phase I unit has a procedure in place to ensure that there are clear parameters for the dose escalation decision, that this is documented and that there is a system in place to prevent dose escalation with an inappropriate set of data. The NPRA expects the unit to ensure that the protocol, whether written by the sponsor or the Phase I unit itself, includes the number of subjects required to complete a cohort, details of the proposed data to be used for the decision and clear stopping rules. If this is not clear in the protocol, then this must be addressed in a separate document (agreed between the unit and the sponsor). There must be clear instructions not to proceed if dose escalation limits are violated, or until an appropriate substantial amendment receives regulatory and ethical approval.

Many clinical trials will be designed to incorporate dose leaders, i.e. dosing of subjects 24 hours apart, usually one placebo and one active. If the unit is involved in randomisation, then there must be a procedure in place to ensure that when using this approach dose leaders are not all randomised to placebo. Appropriate unblinded

personnel (e.g. pharmacy staff or named individuals) should be identified to check the assessment of dose leaders prior to dosing and this should be documented.

The trial file must contain and clearly reflect the data reviewed and the decisions taken. It must also be clear what data will be reviewed and by whom, for example, the sponsor or representative may be reviewing unblinded data not available to the Phase I unit. It is expected that the decision to dose escalate is approved by the Sponsor and the PI and that this decision and the approvals are documented. The PI may delegate this task to another suitably qualified investigator involved in the clinical trial, but this delegation must be formally authorised and documented before this individual performs the activity. The decision surrounding dose escalation must be clearly documented before any further subjects are dosed. It should be remembered that the outcome may not always be to escalate (e.g. doses could remain at the same level or be reduced), and these decisions are just as important and need to be documented in the same way.

It is imperative that the data used to make the decision are accurate. Therefore, **all data** used for the dose escalation decision must be subject to quality control procedures.

Where there are multiple sites recruiting in a dose escalation clinical trial and/or the data are being collated elsewhere (e.g. by the sponsor or third party vendor), it is expected that the Phase I unit satisfies themselves that all the data received from outside the Phase I unit are prepared to an equivalent standard as the unit's own procedures (i.e. those that have been assessed during the accreditation inspection by the NPRA). This may be via clarification with the sponsor or directly with the third party vendor. The sponsor and all PIs from each of the recruiting sites should be involved in the dose escalation decision. Therefore for a trial to be run to accreditation standards, the sponsor should ensure that the data they supply (either themselves or from a third party vendor) are also subject to quality control procedures.

Similar quality control procedures should also be considered for other important safety decisions, such as those made by a Data Monitoring Committee etc.

MEDICAL EMERGENCIES AND FACILITIES

- 3. An agreement with the hospital for supporting emergencies arising from the clinical trials performed by the Phase I unit or the ability to demonstrate communication and notification of trial information (e.g. dosing times) with the hospital's emergency teams. The hospital resuscitation committee, emergency response team and the Intensive Care Unit (ICU) staff (as applicable) must be**

aware of the accredited unit, the nature of the research (e.g. FIH, Biologicals etc.), and that they could be referred patients from the unit at any time.

- 4. An emergency trolley must be available that is easily and rapidly accessible. There must be a trolley in each main area, which can be moved quickly to where it is needed. The emergency trolley must be stocked as per the appendix IV and carry as a minimum:**
 - a. Oxygen and delivery apparatus**
 - b. Equipment for procedures such as cannulation and suitable fluids for IV infusion**
 - c. Supraglottic airway devices (e.g. laryngeal mask airway, i-gel)**
 - d. Self-inflating bag, or equivalent, for assisted ventilation**
 - e. Suction equipment**
 - f. Defibrillator**
 - g. Equipment for tracheal intubation and emergency cricothyroidotomy should be available for use by appropriately experienced personnel or a responding emergency team only.**

Emergency Trolley

Based on the number of wards/beds and the layout of the unit, there must be enough emergency trolleys (or acceptable alternative, such as a grab bag) to ensure they are easily and rapidly accessible. The emergency trolley contents should reflect the list of emergency medicines in appendix IV. Trolley contents may vary between units because they may be standardised throughout a specific hospital and thus staff in a given unit are unlikely to have been trained to use all items. Units may want to take the guidance of the hospital or contracted resuscitation officer to ensure that trolley content are appropriate. Where it is decided that there will be deviations from the list of emergency medicines, this should be documented and retained for request upon inspection.

In some units the equipment or medicines that are not required to be readily available are held in alternative locations (e.g. ward drugs cupboard or pharmacy). Where this may be the case there should be clear consolidated oversight of where all list of emergency medicines contents are held or documented justification if not required. Also there should be documentation of any checks when there is a change to either the list of emergency medicines requirements.

- 5. There must be a documented weekly check of the contents of the emergency trolley, including regular checks of the expiry dates for medication and equipment. If the emergency trolley or the emergency drug box is sealed then the tamper proof seal should be checked weekly.**
- 6. Continuous monitoring equipment must be available to include ECG, pulse oximetry, vital signs such as blood pressure, heart rate and temperature.**
- 7. Beds used for dosing days must be able to be tilted and adjusted for height.**
- 8. Alarms must be placed in any areas likely to be occupied by subjects (e.g. showers, toilets, ward(s) and recreational areas(s)) and these must be regularly tested (and the testing documented).**
- 9. Staff must be able to open the toilet/bathroom doors from the outside in an emergency.**
- 10. A robust (and tested) arrangement for immediate maintenance of life support (i.e. resuscitation and stabilisation of subjects in an acute emergency) and onward transfer of subjects to hospital, where necessary**
- 11. All staff must undergo periodic testing of emergency scenarios within the unit. This testing must be documented. For those staff in contact with subjects, they must attend at least one scenario a year in addition to any scenarios conducted as part of a staff members life support certification (e.g. ALS/ BLS or equivalent).**

Medical Emergency Rehearsal/Periodic Testing

Phase I unit personnel must be trained and prepared to identify when a subject is becoming unwell and to initiate treatment of a medical emergency if it arises. Drills or mock scenarios ensure that those who do not handle medical emergencies on a daily basis maintain their knowledge and skills; for this reason, such training is imperative. One method of doing this is to undertake scenarios that cover a variety of situations (e.g. cardiac arrest, anaphylaxis etc.) that allow staff to simulate what they would do in an emergency. Consideration should be given to when these scenarios are rehearsed in order to include the possibility of involving night/agency/bank staff, busier times when volunteers are in the unit and the various locations around the unit. Some units have also incorporated testing of their unblinding

procedures into the scenarios; this is recommended, but is not expected if there is separate testing of the unit's unblinding procedures.

These scenarios should be seen as learning opportunities and must be documented and distributed so that any learning points can be shared with all the clinical team, whether they attended the scenario or not. Any corrective and preventative actions following the scenario should be followed up and documented. Attendance at this training must be documented and tracked to ensure that all staff regularly take part. Although the number of training sessions will vary according to the size of the unit, it is expected that individual members of staff who are in contact with subjects should attend at least one session annually. The minimum frequency of training required for individual members of staff should be defined in the unit's procedures. It should also be noted that these scenarios are specific to the unit and types of trials they undertake etc. therefore are in addition to any scenarios conducted as part of a staff members life support certification (e.g. ALS/BLS or equivalent).

During an accreditation inspection the NPRA may ask for a demonstration of an emergency scenario, along with testing of a transfer to hospital. Some units have been able to utilise the local ambulance service and transfer the inspectors to hospital as part of the scenario, whereas others have driven to the hospital themselves. The inspectors will leave it up to the unit to decide how best to demonstrate this process.

Procedures should be in place to cover the transfer of a subject to hospital, and also to ensure that the treating physician has appropriate information about the IP and the clinical trial, next of kin details and unblinding information where relevant. It is the accredited unit's responsibility to ensure the most likely method of transfer to hospital has been tested, or there are documentation supporting expected transfer times.

The nature and extent of the medical emergency procedures or medical emergency scenarios will vary depending on the type and location of the unit as this may involve the interaction with the hospital resuscitation team or paramedics during some of the scenarios. However, consideration should be given to providing a minimum level of scenario training for all staff who have direct contact with subjects to ensure they can identify and manage any emergencies within their remit; even if their role is only to open doors, make telephone calls or receive/direct the paramedics/resuscitation team etc.

Emergency scenarios specific to a trial may also be identified via the trial's risk assessment and these should be incorporated into trial specific training as necessary.

There should be a system to track emergency scenario training to ensure that it is being undertaken at the frequency required in the written procedures, that a variety of appropriate scenarios are taking place (e.g. different events, locations and times) and that relevant staff are sufficiently involved in the training.

STAFF

- 12. Documentation that demonstrates that medical doctors are authorised to act as principal investigator – for example, as described by their job description (or other formal documentation approved by appropriately appointed personnel, such as the risk assessment, an authorisation statement, etc.), and supported by a *curriculum vitae* and training record. It is expected that Principal Investigators have relevant qualifications, training and clinical experience.**

For medical doctors that wish to undertake FIH trials , in addition to the above it is expected that Principal Investigators for FIH trials have relevant clinical experience in running Phase I trials, plus a post-graduate qualification, such as a Diploma in Human Pharmacology, MSc in Clinical Pharmacology or equivalent. The Diploma in Pharmaceutical Medicine would only be considered acceptable where it is supported by experience in FIH trials.

Where the unit does not directly employ the PI, there must be a mechanism for the unit to assess the trial and the suitability of the PI, plus their research team (as applicable) and ensure there is responsibility formally assigned that meets the above qualifications, training and experience where gaps are identified (e.g. use of a Phase I review committee and expert advisor, information is available on expectation in the associated guidance).

Principal Investigator (PI) Requirements

PI Qualification, training and experience, including relevant post-graduate qualification for FIH trials

The expectation is that the unit has formal procedures in place that specify what investigators require in terms of qualifications, training and experience in relation to the types of trials for which they are “authorised” to act as a PI. Therefore, it is the units’ responsibility to assign a suitably qualified PI; it is not the responsibility of the NPRA or IEC to undertake this assessment when authorising/approving the clinical trial.

For FIH trials, the PI is required to hold a relevant post-graduate qualification; this is to provide assurance that the PI is able to review pre-clinical data, assess the pharmacology and subsequent aspects such as the proposed starting dose, dose escalation proposal/stopping criteria etc. They will thus be able to ensure that they have all the relevant information from the sponsor and be able to interpret it before dosing subjects. Relevant post-graduate qualifications include: Diploma in Human Pharmacology, Completion of Speciality Training in Clinical Pharmacology and higher degrees in pharmacology. Qualifications such as Member of the Royal College of Physicians (MRCP) and Completion of Specialty Training in Pharmaceutical Medicine (PMST) are highly desirable, but are not considered to be sufficient. The Diploma in Pharmaceutical Medicine would only be considered acceptable where it is supported by experience in FIH trials.

It is acknowledged that for some units the PI is not directly contracted by the unit (these individuals are commonly referred to as “visiting researchers”); in these circumstances, the unit must have a process in place to assess the trial and the suitability of the PI, plus their research team (as applicable). This process is described below in section “Phase I Review Meeting/Named Expert Advisor”.

Where units have contracted medical doctors to act as a PI on FIH trials, they should be identified as key personnel and will thus be named on the accreditation certificate. Where units do not directly contract the PI i.e. they are a “visiting researcher”, the unit should nominate a named representative to take responsibility for assessing the suitability of PIs on behalf of the unit (this may be the Director of the unit, the Chair of the Phase I Review Meeting etc.)

Scientific Review Panel (SRP) Exemption

It is recognised that there are a number of PIs that, although they have no formal post-graduate qualification, have a significant amount of experience in pharmacology (and are often involved in teaching the post-graduate courses) and therefore could be exempt from the requirement to hold a post-graduate qualification. In these cases, PIs will have to demonstrate that they are sufficiently experienced and submit a rationale for their exemption to the Scientific Review Panel (SRP) for an independent peer review. There may be occasions where a PI may only be relevantly qualified in their field of expertise (e.g. vaccines, oncology etc) and as such only able to act as a PI for FIH trials in their field of expertise;

again this will be submitted to the SRP for assessment. An exemption can also be requested for a PI who is a “visiting researcher”.

Phase 1 Unit may submit variation application to NPRA when the exemption to the PI was granted by the SRP.

Where the PI is a “visiting researcher”, and thereby assessed by the unit, this exemption can also apply for those with a significant amount of experience in conducting FIH trials. See the section “Phase I Review Meeting/Named Expert Advisor” below for further details. In these cases the “visiting researchers” will also be added to the accreditation certificate in addition to the units named representative.

However, medical personnel and investigators are required to practice strictly within the limits of their competence.

Phase I Review Meeting and Named Expert Advisor

It is acknowledged that in some trials units (mainly academic units), in addition to core staff such as nurses, technicians and possibly medical doctors who have the required qualifications, training and experience in conducting Phase I trials (including FIH), there will be other “visiting researchers” utilising the facilities for their own trials. These “visiting researchers” while being experts in their therapeutic area, and possibly later phase trials, may want to conduct their own Phase I trial, but may not meet all the requirements of the accreditation scheme for being the named PI (for example, they may not have the relevant post-graduate qualifications in pharmacology to be a PI for a FIH clinical trial). Funding applications, sponsor and/or publication requirements may mean that it is not appropriate for another medical doctor that is suitably qualified to be the named PI for the trial. In these circumstances, there should be a formal mechanism for the review of any requests to use the units’ facilities in order to identify those clinical trials that fall within the remit of the accreditation scheme. This mechanism should ensure that these trials are adequately assessed by relevant experts for suitability of the trial and the research staff, including the PI. Any gaps in the trial design/logistics and suitability of trial staff or PI should be captured and mitigations implemented, prior to agreement to support the trial at that facility.

To address this aspect, the unit should have in place a formal Phase 1 Review Meeting responsible for the review and risk assessment of Phase I clinical trials and the personnel involved in conducting the trial, with a particular emphasis on the suitability of the PI.

In order for a Phase 1 Review Meeting to be accepted under the terms of the accreditation scheme, a written procedure is required identifying the terms, remit and activities of the meeting (this can be in the form of a Standard Operating Procedure (SOP), terms of reference document, member charter etc.) This written procedure would have to include:

- Identifying relevant trials required to be submitted to the Phase 1 Review Meeting (i.e. Phase I trials).
- A minimum quorum of members. These members must have the relevant expertise to assess a Phase I trial (e.g. be able to review the IB, understand the preclinical data including calculating the starting dose/dose increments, assess the pharmacological aspects of the trial etc.) Members could thus be, for example, pharmacologists, toxicologists or a unit representative. In addition, in order to meet the accreditation requirements, at least one member of the quorate should be a medical doctor experienced in Phase I clinical trials and who meets the requirements to act as a PI for FIH trials in their own right.
- The minimum required experience/qualification of the meeting members, plus provision to invite any experts/specialists if the meeting do not have the relevant experience themselves in a particular therapeutic area or specialty (e.g. paediatrics, oncology etc.)
- A clear conflict of interest policy if the requesting researcher is a member of the meeting (i.e. the requesting researcher/PI can participate in discussions; however, cannot influence the overall decision by the meeting).
- A formalised mechanism for what documentation the meeting requires for review, how these will be circulated and the provision of comments to the meeting from non-attending members (or the allocation of a suitably qualified delegate). Documents may include (but will not be limited to): the protocol, IB/other safety information, regulatory/ethics documents, risk assessment, Phase 1 review meeting application form, CVs.
- How the review of the proposed Phase I trial and the meeting's decisions and recommendations will be documented. This will include the full risk assessment as per the accreditation scheme requirements (and as detailed earlier in this guidance document) and in addition include the review of the requesting researcher/PI and research team, detailing any identified gaps in expertise and their mitigation. The output of the meeting may be the formal risk assessment or a supporting named document complementing the risk assessment.

- The process for the meeting's continued involvement throughout the lifecycle of the trial, including their oversight or input into amendments and ongoing safety updates, dose escalation decisions etc. This could also include any requirements for the submission and approvals of final or updated documents if the meeting has made a decision based on draft pre-clinical data or a draft protocol.
- The requirements for reviewing the requesting researcher's/PI's qualifications and experience in relation to a Phase I trial and in particular, a FIH trial. For example, if the requesting researcher/PI meets the accreditation scheme requirements for a FIH clinical trial, the meeting could approve the investigator per se. However, should the requesting researcher/PI not meet the minimum requirements as detailed in the accreditation scheme, the meeting must identify the gaps in the PI's expertise and assign a "named expert advisor" who will take responsibility to cover those gaps. The meeting must clearly identify the remit and oversight of the "named expert advisor" and how this oversight will be documented. The meeting itself may also decide to take a more active role in this type of trial to ensure there is appropriate oversight of key aspects such as dose escalation decisions, ongoing safety reviews etc. The requirement for a "named expert advisor" and any oversight activities should be documented within the meeting's risk assessment report. Documentation to verify compliance with the identified mitigations throughout the course of the trial and the meeting's role would also be required as evidence of compliance with the risk assessment.

Where the meeting has identified gaps/risks in certain areas of the trial and has recommended actions to mitigate them (for example, the meeting may have identified the need for a "named expert advisor" to provide advice to the PI or to make specific decisions), there must be clear documentation that the PI accepts those recommendations for the trial to go ahead and there must also be documentation that these conditions were met during the course of the trial.

It is acknowledged that in some specialist therapeutic areas (e.g. oncology) there are a number of PIs that, although they have no formal pharmacological post-graduate qualification, they have a significant amount of experience in phase I trials including FTIP and therefore should be exempt from the requirement to have a relevant pharmacology post-graduate qualification when undertaking these types of trials. In these cases, with the support of the Phase I meeting, the PI can apply for the formal exemption via the FPM, as detailed in the guidance above.

However, there should be clear mechanisms for how the meeting ensure that less experienced PIs do not use the meeting process as an alternative to gaining an approved post-graduate qualification. For example, the “named expert advisor” approach is only acceptable where the requesting researcher/PI is doing a “one-off” or occasional Phase I trial. There should be a mechanism in place at the unit to allow for less experienced PIs intending to conduct subsequent or numerous FIH trials, to be formally mentored while working to gain their post-graduate qualification.

The PI would still retain their legal responsibility for the conduct of the trial as stated in the legislation, therefore, it is expected that the PI, the meeting and the “named expert advisor” (where applicable) understand their obligations, accountability and responsibility, and this should be documented (e.g. in an agreement or the risk assessment etc.) Everyone should be aware of, identify and acknowledge their limitations in respect of the trial.

Note: The ‘Phase I Review Meeting’ approach is required for units where there are researchers not contracted by the unit that request to undertake clinical trials including Phase I trials within the unit. Units that contract medical doctors that are appropriately authorised to act as PIs for Phase I trials (i.e. as part of their job description) and are allocated to trials do not require this meeting. Units may wish to implement a meeting of this type as routine to support the risk assessment process. However, this should not be used as a mechanism to allow a unit’s employed PIs who do not meet the accreditation requirements to act as PIs on FIH trials. It is also considered good practice (and is therefore recommended) that if units undertake clinical trials in specialist therapeutic areas, they implement a review meeting for these types of trials and invite a therapeutic expert to address any identified gaps in experience.

13. Documentation that demonstrates that appropriately trained and experienced staff are available on dosing days. During the conduct of FIH, medical doctors trained to Advanced Life Support (ALS) standards and experienced in handling medical emergencies must be present during and following dosing for a defined period. In addition to theoretical knowledge, the medical doctors must have relevant and recent experience of handling medical emergencies. Units may approach this in a number of ways, for example:

- **The units employed (or core staff) Clinical Research Physicians (CRP) are ALS trained^a and may participate on an ongoing basis in periodic clinical attachments**

involving participation in a hospital resuscitation team rota to ensure continued exposure to identifying and handling real medical emergencies^b

Or

- **Appropriately trained clinicians with up-to-date emergency medicine experience may be brought in to the unit on a contract basis during dosing days. These contract staff must also be trained in ALS, the study protocol, unit procedures and GCP. The contractor would not be expected to take on the role of the Principal Investigator and must be appropriately supervised whilst in the unit. Indemnity arrangements made by the Sponsor and/or unit must also apply to the contract medic.**

Or

- **Phase I unit may be located within a hospital; with critical care facilities. The unit will have 24-hour access to the hospital emergency response team, who can arrive at the unit within minutes of an emergency.**

^aFor paediatric Phase I trials an equivalent paediatric life support training (for example, Advanced Paediatric Life Support (APLS) or European Paediatric Life Support (EPLS)).

^bWhere the unit uses its employed (or core) CRPs to provide cover in a medical emergency, the CRPs must be able to demonstrate appropriate training and experience in handling medical emergencies. A procedure must be in place to address the assessment of continuing competency in this area (e.g. it may be achieved by peer review, audit or other means). This continuing assessment must be documented and countersigned by the assessors. Evidence must be kept to document exposure to medical emergencies in order to demonstrate that they remain experienced and competent to handle such emergencies.

FIH trials - additional requirements for availability of medical doctors during and following dosing: requirement for ‘relevant and recent experience of handling medical emergencies’

FIH trials require medical doctors to have ‘relevant and recent experience of handling medical emergencies’. There are several ways that this can be met. A Phase I unit that is based in a hospital and can rely on calling the hospital’s resuscitation team in an emergency

clearly meets this requirement. For those units not based in a hospital, this can be addressed in several other ways:

- The unit's medical doctors also work part-time within clinical practice (for example, in the emergency department or Intensive Care Unit (ICU)). It is expected that a training log is maintained by these medical doctors to list their experiences within the clinical setting, with sufficient detail, to demonstrate that their experience remains relevant and recent. Honorary contracts with the hospital or other contractual arrangement for this should be in place.
- Phase I units have contracted in medical doctors with relevant and recent experience for the dosing days. The NPRA would expect the Phase I unit to have a contract in place with these medical doctors and the Phase I unit should have assessed their suitability for the role. In addition the Phase I unit must ensure that the contracted medics have received adequate training in GCP, the clinical trial and unit procedures.
- Phase I units have also employed medical doctors who have recently worked in relevant areas of clinical practice. Experience must remain recent therefore these medical doctors will be required to demonstrate how this is achieved.

These medical doctors will not necessarily be PIs or investigators, although in some cases there will be overlap. The Accreditation Scheme requires that a medical doctor able to manage an acute emergency is present on dosing days for FIH trials, but this does not have to be the PI.

Where there is a requirement to have a specialist medical doctor present (be this for a FIH or with relevant expertise for the therapeutic indication etc, as specified in the protocol or risk assessment) in addition to the unit minimum staffing requirements, there should be documented evidence of when these specialists were present on the unit to verify they were present for the duration specified. For example, some units use a sign in/out register or the security tag date/time logs for their medical doctors to show their compliance with the risk assessment mitigation or minimum staffing requirements procedure.

14. Documentation to demonstrate that there are sufficient numbers of trained and experienced staff employed by or contracted to the unit for all activities conducted by the unit (including appropriate numbers of staff with adequate training to handle medical emergencies). There must be sufficient cover for dosing days and overnight stays. The unit must have in place a policy or SOP that stipulates the minimum staffing levels during clinical conduct of the study.

Sufficient trained and experience staff availability

Acceptable minimum staff levels

Although the accreditation scheme requires Phase I units to have a procedure defining the minimum number of staff, the NPRA do not stipulate a specific number. The unit's procedure must take into consideration the number of staff required to manage a medical emergency, should it arise. The procedure should also consider the levels of life support training and the use of agency/bank staff or, in the case of non-commercial units, visiting research teams. Staffing levels should also be modified in relation to the number of subjects on the unit, the types of clinical trials being undertaken and the number of wards that are occupied. The unit should be able to provide evidence that the minimum staffing levels stipulated in their procedures or trial specific documents e.g. protocol or risk assessment have been complied with. The protocol or risk assessment may stipulate an increase in the staffing level above the minimum staffing levels stipulated in the unit procedures, but must not reduce them.

The procedure should encompass both nursing and medical staff and also give consideration to the flexibility for the range and types of trials that may be undertaken in the unit. However, it must be clear what the minimum requirements are and how they differ for FIH trials and how increased or additional staffing will be identified (i.e. via the risk assessment).

Resourcing and allocation/delegation of staff

It is important that the unit has available trained and experienced staff (both medical doctors and nurses etc.) to undertake the trials they are conducting. Therefore, the resourcing and allocation of staff to the trials is an important aspect of the unit's day to day function. For units where there are visiting research staff (for example, in a non-commercial facility where researchers can undertake their trial in the unit), this must encompass the unit's review and assessment of not just the trial, but also all the visiting staff including the PI. This is important to ensure the PI is suitably qualified and that the allocation of resources from visiting staff meets the requirements of the accreditation scheme or is supplemented by core staff.

There should be formal procedures for the allocation and assignment of staff to key protocol tasks. This should encompass mechanisms to ensure that only staff that are trained and competent to perform that activity and have been formally delegated that activity are assigned. Therefore, the person(s) responsible for preparing the document assigning staff (this may be known by many names, for example, duty rota, procedure sheet, study allocation sheet etc.) should use all the available tools (i.e. both general training matrices,

delegation logs or study specific training logs) to identify staff that are trained and competent before allocating them to the activities.

It is imperative that any documents used to record allocation of staff that are derived from the protocol (e.g. that contain the timings of trial tasks) are robust. Therefore, these tools must have a documented validation/QC to ensure they are in compliance with the relevant version of the protocol, otherwise it could lead to breach in protocol (legislation) and potential harm to subjects/trial integrity if safety measurements or assessments are missed.

Consideration should also be given to how the unit deals with unexpected absences. In addition the unit should ensure that it has sufficient resource, for example a 'spare' member of staff that is not allocated specific tasks, so they are able to support the team if there are problems, for example difficulties with a blood draw that may then lead to other blood draws becoming late unless someone else is able to step in and assist

As with any trial, it is expected that the PI only delegates tasks to suitably qualified personnel, therefore, personnel should only be listed on the delegation log if they are trained in GCP, competent in the specific task and trained in any study specific procedures (as documented in the various records, e.g. training records or the trial file).

15. Staff that are appropriately and currently trained and assessed as competent to perform the activities that they are assigned to undertake. In addition, for clinical staff this must include initiating resuscitation (i.e. basic airway management and ventilation, i.v. cannulation and fluid therapy, giving adrenaline, CPR and use of a defibrillator or an automated external defibrillator (AED)). Annual updates are required. At a minimum clinical staff should receive Basic Life Support (BLS) Training and annual updates (or equivalent paediatric life support training (e.g. PILs) for units that undertake paediatric trials).

Varying job titles and descriptions have caused confusion about the definition of clinical staff in relation to the accreditation scheme. Within the accreditation scheme, the meaning of "clinical staff" equates to at a minimum, the nurses, medical doctors and those staff that would be responsible for managing the subjects' care whilst they are in the unit, and therefore, the staff who would have a direct role in the management of medical emergencies. This may vary depending on the set-up of the unit, for example, it could encompass all the nurses and clinical technicians etc. especially where units are not located within a hospital or key staff who will be formally allocated responsibility for dealing with the medical emergencies (i.e. an allocated in-house resuscitation team that will manage the subject until

the paramedics/hospital resuscitation team arrive). This should include any on-call or “bank” medical doctors or nurses that the unit employs that may have to cover medical emergencies.

Where there may be units that have core staff and also have trials that have a visiting research team, there must be a formal assessment of the research teams qualifications and training in relation to their life support training to ensure they either meet the minimum requirements for the unit, or the unit can ensure that core staff are resourced to the clinical trial to provide this aspect. This must be documented (e.g. as part of the risk assessment).

SUBJECT IDENTIFICATION

16. A procedure to address ‘over-volunteering’.

Over-volunteering

The accreditation scheme requires a formal procedure to be in place to address how the unit will minimise the risk of over-volunteering for healthy volunteers and in some cases volunteer patients (e.g. diabetic or asthma studies). There is no single mechanism to combat this risk, but there are a variety of different activities that combined can reduce the risk of over-volunteering.

The unit should have a robust database that contains a comprehensive list of all the volunteers that have participated in any clinical trials the unit has undertaken, in order to identify the last time the unit has dosed the volunteer. The database should also identify any significant information relating to that volunteer, that may preclude them for use in particular trials. There should be procedures in place to manage the database which must comply with data protection regulations.

In addition, there are various physical examinations and safety assessments that can give indications to whether a volunteer has recently participated in a clinical trial at another unit.

The Phase 1 Unit’s volunteer database should be cross referenced with an established healthy volunteer database to ensure that over-volunteering does not occur in the FIH clinical trial conducted.

Patient trials are slightly more complicated. For the most part, where there is a set of comprehensive medical notes available providing their medical history (i.e. where the patient is identified in clinics or referred by their consultant), there would be no need to use volunteer database. However, there are a group of “patient volunteers” (i.e. they are generally healthy,

but may suffer from mild asthma, diabetes etc. and are responding to an advert) where there are no such suitable medical notes. For these types of subjects (i.e. the volunteer patient), there may be a justification to use volunteer database. Any decision to use medical notes or volunteer database should be documented (e.g. as part of the risk assessment).

When using volunteer database it is expected that units document the checks performed and follow the volunteer database guidance for entering subjects. This currently uses either the national identification number or passport number for foreigner. To ensure the correct information is registered and checked, when using the ID number, evidence should be requested for this to ensure it is the subject's own ID number that has been provided. Units should also consider how they check subjects with dual nationality to ensure they are not listed multiple times using different IDs.

17. A robust procedure to accurately identify subjects. For volunteers this must include utilising photographic identification, thereby verifying the persons identify/existence and ensuring that the person screened is the person dosed.

Photographic Identification

The accreditation scheme requires a formal procedure to be in place to address how subjects will be identified. This may vary depending on the type of trial being performed. For trials using healthy volunteers or patient volunteers (i.e. they are responding to an advert and not being recruited or referred by their treating medical doctor) then the unit has to be sure they can confirm who the subject is and are able to verify that it is the same person that attends all the trial visits. This must be done using a valid form of photographic ID (i.e. photo driving licence or passport). The unit should retain a copy in the subjects' records throughout the duration of the trial to check it is the same person at each visit, and should ideally retain it after completion for evidence of the subjects' existence, especially if there is no other mechanism to verify this. Some units utilise a digital photo which is saved in the subjects' records/volunteer database, this is acceptable to verify the subject at each visit. However, it is also recommended that a copy of the original photographic ID is retained as well (or at a minimum the unique details (i.e. passport or driving licence number.)

18. For FIH, unit is required to confirm the subjects' past medical history according to the protocol. For volunteers, this should be received *via* the subjects' personal doctor, or other medical doctor (such as hospital consultant for patient trials where they are not recruited by their own consultant, therefore have no access to

the medical records for the patient), to provide assurance that inclusion and exclusion criteria are met.

Confirmation of the subjects' past medical history

For all early phase trials using volunteers, it is good practice and therefore highly recommended to obtain confirmation of subjects' past medical history prior to dosing *via* the subjects' personal doctor or other medical doctor (such as a hospital consultant for trials where they are not recruited by their own consultant, therefore have no access to the medical records for the patient) to provide assurance that the inclusion and exclusion criteria are met.

However, for FIH using healthy volunteers, the unit is required to obtain verification and this should be in writing.

It is expected that the procedure for contacting the personal doctor is formalised, clearly documenting how this will be performed, reviewed and documented, including the frequency. Consideration should be given to the various types of trials a unit undertakes and that their requirements are differentiated between (i.e. it is clear when a personal doctor questionnaire is needed or not). Also, there may be occasions where a risk assessment for a particular trial identifies an increased need for vigilance (for example, a personal doctor questionnaire is required in a trial that would not normally require it, or a new/up to date personal doctor questionnaire is needed, or that the personal doctor has access to a certain period of medical history, due to the eligibility criteria required).

19. The unit must also hold the contact numbers for subjects to ensure that they are able to be contacted outside the unit should the need arise. Subjects must also be provided with 24-hour emergency contact numbers for while they are outside the unit.

QUALITY SYSTEM

20. Written Standard Operating Procedures (SOPs) for every aspect of the unit's activities including all the accreditation requirements. These SOPs must specifically include (but are not limited to):

- a. Procedures for handling common medical emergencies e.g. syncope, hypotension, anaphylaxis, cardiac arrest**

- b. Out-of-hours medical cover and contact with sponsor or IP responsible person(s)**
- c. Procedures for handling immediate maintenance of life support (i.e. resuscitation and stabilisation of subjects in an acute emergency)**
- d. Transfer of subjects to hospital, including the provision of all relevant medical information regarding the trial and the subject(s) in question to the hospital**
- e. Training and refresher training, including competency assessments for all key activities, including emergency resuscitation procedures**
- f. Unblinding in an emergency**
- g. Risk assessment and mitigation**
- h. Dose escalation**
- i. Staffing level/resourcing**
- j. Expectation for minimum qualifications, training and experience for key roles and responsibilities (e.g. PIs, nurses, Phase I review meetings etc).**
- k. Minimum staffing requirements**
- l. Subject recruitment, including identification, medical history and over-volunteering**

[Note: This is not an exhaustive list, and units should ensure all activities are formalised adequately, especially where these impact on accreditation requirements.]

Quality System

It is appreciated that units will undertake a variety of studies, ranging from first in human (healthy volunteers and patients) to later phase clinical trials, Advanced Therapy IPs (ATMPs), other early phase trials using both healthy volunteers and volunteer patients etc. Therefore, consideration should be given to ensuring the formal procedures covering the unit's activities, are flexible enough to encompass the variety of trials, while making it clear what the minimum requirements are for meeting the accreditation scheme (i.e. where the requirements differ for Phase I trials, especially FIH trials and those using healthy volunteers or patient volunteers).

Procedures need to ensure that the unit's own local requirements as well as the accreditation scheme requirements are encompassed and followed. Any emergency related procedure (for example, emergency unblinding, emergency alarm buttons, out of hours/emergency phone

numbers etc.) should encompass routine testing, how this is documented, the frequency and any CAPA in the event of failures/issues.

The procedures should stipulate the minimum requirements, but also link into the risk assessment and how any additional or enhanced requirements will be documented for a specific trial.

8.0 APPENDIX II:PROCEDURE/REQUIREMENTS FOR PHASE 1 UNIT INSPECTION

1.0 PROTOCOL AND PROCEDURAL ASPECTS

Points to consider:

- What data is used to make dose escalation decisions. Is this adequate if less than a full cohort
- QC of dose escalation data and interim safety reports
- Clarity of dose escalation and withdrawal criteria
- Documentation of dose escalation decisions
- Knowledge of the PI in relation to pharmacology of the IP
- Risk assessment and contingency planning e.g emergency treatments, specialist medical staff

2.0 ETHICS AND REGULATORY APPROVAL

Points to consider:

- Independence of the Ethics Committee
- What documents does the Committee review. Approval of generic screening consent forms
- Approval of advertising
- Documentation of approvals
- Process for submission for Ethics Committee approvals. Updating and maintenance of Ethics Committee documentation
- ICH GCP compliance statement of the Ethics Committee
- List of members of the Ethics Committee
- Annual reporting to the Ethics Committee.

3.0 QUALITY ASSURANCE AND SOPs

Points to Consider

- Written procedures for every aspect of the study process (SOPs)
- Organisation and independence of the QA group
- Training on SOPs, GCP and also specific protocols
- Audits on vendors and suppliers

4.0 INVESTIGATOR MASTER FILE

Points to Consider

- Identification and use of source documents
- Storage of medical records
- Long-term archive arrangements
- Documentation of meetings
- Delegation log in place and signed
- Use of Direct Electronic Data Capture methods

5.0 PERSONNEL

Points to Consider

- SOP for minimum staffing levels during clinical conduct and medical supervision on dosing days
- Relationship of the Investigator with the Sponsor company
- Adequate staff resources
- Basic life support and advanced life support training
- Qualifications of the Investigators
- Qualification of Bank/Agency staff
- Management of Agency/Bank staff
- Continuous training on relevant area

6.0 FACILITIES

Points to Consider

6.1 Emergency Procedures and Equipment

- Availability and maintenance of emergency medicines and equipment
- Emergency contact numbers provided to the volunteers
- Procedures in case of an emergency
- Alarm points
- Agreement with the local hospital(s) for any services provided
- Fire evacuation procedures

6.2 General Facilities

- Security of the facility with respect to unauthorised or limited access
- Back-up power supply
- Storage of samples. Monitoring of the fridges and freezers
- Maintenance, service and calibration of instruments/equipment
- Facilities for archiving, laboratory and pharmacy.

6.3 Volunteer Care

- Procedures for testing for use of illegal drugs (drugs of abuse)
- Measures in place to ensure compliance of the volunteers with the protocol
- Monitoring of subjects
- Facilities for meals. Documentation of meals
- Leisure facilities for lengthy stays/overnight stays
- Identification of subjects during their stay
- Documentation of medical history

7.0 SAMPLING

Points to consider

- Documentation of processing of samples within the unit prior to shipment to the laboratory
- Facilities equipped and resourced to handle the capacity of samples
- Procedures for collection of urine samples
- Procedures for sample management e.g. collection, processing, consideration for missed and late samples, aliquoting, labelling, tracking, storage and shipment
- Clocks – easily visible and synchronised.

8.0 INVESTIGATIONAL PRODUCT

Points to Consider

- Authorisation/Licence(s)
- Blinding, if applicable
- Storage and access control
- Packaging and labelling
- IP administration
- Compliance with the randomisation list, if applicable
- IP accountability

9.0 RECRUITMENT AND CONSENT

Points to Consider

- Recruitment strategies
- Volunteer database
- Collection and verification of volunteer medical histories
- Contact with the subject's primary physician/family doctor
- Procedures to prevent 'over-volunteering'
- Routine screening procedure
- Subject records
- Procedures taken to verify the identity of the volunteers
- Procedures for payment
- Procedures for taking consent
- Training of the recruitment staff
- Recruitment of staff from the facility/institution

10.0 CONTRACTS

Points to Consider

- Contracts in place prior to study start
- Management and documentation of collaborations with other departments/organisations

11.0 INSURANCE AND INDEMNITY

Points to Consider

- Provisions in place for insurance and indemnity
- Indemnification of the investigator
- Professional indemnity insurance for nurses, if applicable

12.0 CONFIDENTIALITY

Points to Consider

- Confidentiality agreements for Agency staff, consultants etc
- Procedure to ensure volunteer identifiers do not leave the unit (e.g on sample labels, adverse event documentation etc)

13.0 ADVERSE EVENTS

Points to Consider

- Recording of adverse events
- Follow- up and counselling
- SUSAR reporting to Ethics Committee/Regulatory Authorities
- SUSARs information provided to investigator(s)

9.0 APPENDIX III: COMMON FINDINGS

The most common findings from Phase I Accreditation Inspections are listed below:

- Issues with the dose escalation process is by far the most common finding from these inspections, in particular:
 - Decisions to escalate not documented, or approval documented post the next dose level
 - Lack of clarity with respect to who took the escalation decision
 - Data not provided with escalation decision documents
 - No quality control (QC) of data used to make escalation decisions
 - No clear procedure for handling dose escalation studies.

- No formal procedure for risk assessment and risk management/mitigation
- Failure to adequately document and demonstrate risk mitigation activities
- Failure to update the risk assessment and mitigation based on new information (new IB, protocol amendments)
- Emergency scenarios are inadequate i.e. too infrequent so that not all staff receive regular training, or only one medical emergency is rehearsed. Also a lack of follow-up and preventative action for any issues identified during the scenarios
- Training records for agency/bank staff or consultant experts were incomplete or missing
- Inadequate procedures for contacting medical doctors in an emergency outside of normal working hours, i.e. there were no regular documented tests of the system or during inspection the inspectors were unable to contact a medical doctor out of hours
- Expired or missing items on the resuscitation trolley
- No formal procedure to address over-volunteering, or the steps taken to avoid over-volunteering have not been documented
- Incorrect dosing of subjects, due to a lack of adequate procedures and resources
- Inadequate documentation to verify that the staffing requirements defined in the risk assessment had been met or verification that the stated recruitments were not met.
- Lack of robust procedures for the scheduling to ensure all protocol assessments were performed and that staff allocated were suitably trained and competent.

10.0 APPENDIX IV: LIST OF EMERGENCY MEDICINES

Inj. Atropine 1mg	Inj.Heparine 1000iu/5mls
Inj. Adrenaline 1mg	Inj.Heparine 5000iu/5mls
Inj.Esmolol 100mg/mls	Inj.Labetolol 25mg/5mls
Inj. Sodium Bicarbonate 8.4%(50mls)	Inj.Hydralazine 25mg
Inj.CalciumGluconate 1g/10ml	IV Noradrenaline 4mg
Inj.Calcium Chloride 100mg/mls	Inj.Naloxone 0.4mg/mls
Inj.Lignocaine HCL 2%/100mg	IV MDI Salbutamol 100mcg
Inj.Verapamil 2.5mg/mls	IV Promethazine 50mg/2ml
Inj.Water For Injection 10mls	IV Chlorpheniramine 10mg/ml
Inj.Ephedrine 30mg/mls	Inj.Flumazenil 0.5mg/5ml
Inj.Dexamethasone 4mg/mls	Inj.Neostigmine 2.5mg/ml
Inj.Phenylepherine 1%/10mg/mls	Normal Saline 0.9%
Inj.Dextrose 50%(10mls)	Dextrose 5%
Inj.Hydrocortisone 100mgm	Dextrose 10%
Inj.Frusemide 20mg/2mls	Dextrose Saline
Inj.Dopamine 200 mgm	½ Dextrose Saline
Inj.Dobutamine 250mgm	Voluven
Inj.Amiodarone 150mg/3mls	Hartmanns Solution
Inj.Adenosine 6mg/2mls	Gelafundin
Inj.MagnesiumSulphate 2.47gm/5ml	Compound Sodium Lactate (1L)
Inj.SodiumNitroprusside	Gelaspan (500mls)
Inj.GTN 50mg/10ls	Mannitol
Inj.Digoxin 0.5mg/10mls	