



*Your Global Solutions in One Nation*

# **MALAYSIAN PHASE I CLINICAL TRIAL GUIDELINES**

**Endorsed by the National Committee for Clinical Research**

# **Table of contents**

<b>Abbreviations</b>	<b>6</b>
<b>Foreword</b>	<b>8</b>
<b>List of expert panel members</b>	<b>10</b>
<b>1: Introduction</b>	<b>12</b>
<b>2: Developing a new medicine</b>	<b>13</b>
2.1. First-in-Human trial	15
2.2. Subsequent trials	15
<b>3: Reviews and approvals in Phase I clinical trials</b>	<b>16</b>
3.1. National Pharmaceutical Regulatory Agency (NPRA)	17
3.2. Scientific Review Panel (SRP)	17
3.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)	17
<b>4: Risk assessment</b>	<b>18</b>
4.1. All investigational products (IPs)	18
4.2. Higher risk IPs	18
4.3. Other factors	19
<b>5: Risk management</b>	<b>20</b>
5.1. Starting dose	20
5.2. Increasing the dose	21
5.3. Administration of doses	21
5.4. Facilities and staff	21
5.5. Procedures	24
5.6. Subjects	24
<b>6: Safety record of Phase I trials</b>	<b>25</b>
<b>7: Protocol and Investigator’s Brochure (IB)</b>	<b>26</b>
<b>8: Contracts</b>	<b>28</b>
<b>9: Trial subjects</b>	<b>29</b>
9.1. Recruitment	29
9.2. Monitoring overexposure	30

9.3. Special populations	31
9.4. Payments	32
9.5. Obtaining informed consent	33
9.6. Screening	34
9.7. Timing of recruitment and screening	34
9.8. Identification	35
9.9. Informing the subject's personal doctor	35
9.10. Safety	35
9.11. Follow-up	35
<b>10: Pharmacy</b>	<b>37</b>
10.1. Premises, facilities and equipment	37
10.2. Storage	37
10.3. Staff	38
10.4. Types of work	38
<b>11: Investigational products</b>	<b>39</b>
11.1. Manufacture	39
11.2. Documents	39
11.3. Records	39
11.4. Supplying the investigator	39
11.5. Transport to the trial site	40
11.6. Accountability at the trial site	40
11.7. Recall	40
11.8. Randomisation	40
11.9. Emergency unblinding	40
11.10. Quality management	41
<b>12: Management or handling of IP</b>	<b>42</b>
12.1. Requirements	42
12.2. Responsibilities	42
12.3. Releasing IP prepared by the pharmacy	42
<b>13: Resuscitation procedures, equipment, medicines and training</b>	<b>44</b>

13.1. General procedures	44
13.2. Resuscitation equipment and medicines <sup>(14)</sup>	44
13.3. Antidote	45
13.4. Resuscitation training	45
<b>14: Confidentiality</b>	<b>46</b>
14.1. Sponsors	46
14.2. Trial subjects	46
14.3. Personal Data Protection Act	46
14.4. Malaysian Guidelines on the Use of Human Biological Samples for Research	47
<b>15: Compensation, indemnity and insurance</b>	<b>48</b>
15.1. Compensation	48
15.2. Indemnity	48
15.3. Clinical trial insurance	48
<b>16: Safety reporting</b>	<b>49</b>
<b>17: Pathology laboratory</b>	<b>50</b>
17.1. General	50
17.2. Premises, facilities, equipment and procedures	50
17.3. Staff	51
<b>18: Data Management, statistics, report and publication</b>	<b>52</b>
18.1. General	52
18.2. Data management	52
18.3. Statistics	52
18.4. Report and publication policy	53
18.5. Staff	53
<b>19: Essential documents, trial master file and archiving</b>	<b>54</b>
19.1. Trial master file	54
19.2. Quality of documents	54
19.3. Storage of documents	54
19.4. Duration of storage	55
19.5. Disposal of documents	55

<b>20: Project management and monitoring</b>	<b>56</b>
20.1. Qualifications of the project manager and monitor	56
<b>21: Quality management</b>	<b>57</b>
21.1. Quality system	57
21.2. Quality control	57
21.3. Auditors	57
21.4. Audits	58
21.5. Sponsor’s auditors	58
<b>Appendix 1. Preclinical Information to be considered for FIH clinical trials</b>	<b>59</b>
<b>Appendix 2: Process for initiating Phase I (including FIH and First Dose in Human) clinical trials in Malaysia.</b>	<b>61</b>
<b>Appendix 3: Scientific and medical literature</b>	<b>63</b>
<b>Appendix 4: List of custodians</b>	<b>64</b>
<b>Glossary</b>	<b>65</b>
<b>References</b>	<b>66</b>
<b>Acknowledgment</b>	<b>67</b>
<b>Disclosure statement</b>	<b>67</b>

## Abbreviations

AED	Automated external defibrillator
ALS	Advanced Life Support
BLS	Basic Life Support
CGTP	Cell and Gene Therapy Products
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	Clinical Research Physicians
CTEAG	Clinical Trials Expert Advisory Group of the Commission on Human Medicines
CTIL	Clinical Trial Import License
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
DCA	Drug Control Authority
ECG	Electrocardiogram
EMA	European Medicines Agency
FIH	First-in-Human
GCP	Good Clinical Practice
GMM	Genetically Modified Microorganisms
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
MABEL	Minimal Anticipated Biological Effect Level
MDB	Medical Device Board
MRSD	Maximum Recommended Starting Dose
NCE	New chemical entities
NOAEL	'No-observed-adverse-effect' Dose Level
NPRA	National Pharmaceutical Regulatory Agency
NSCERT	National Sub-Committee for Ethics in Stem Cell Research and Therapy
OSHA	Malaysian Occupational Safety and Health Act
PD	Pharmacodynamic
PET	Positron Emission Tomography

PICS	Pharmaceutical Inspection Co-operation Scheme
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction

## Foreword



### A message from the Minister of Health Malaysia

For over 20 years, Malaysia has successfully gained experience in conducting clinical trials by establishing and constantly improving its facilities, processes, regulations and research competent staff. The current Malaysian Economic Transformation Program (ETP) targets clinical research as one of its main drivers in economic growth. In line with this, the Ministry of Health is focusing on streamlining the processes, expanding its experience, facilities and training in the conduct of Phase I clinical studies.

Phase I trials, especially first-in-human trials play a crucial role in the development of medicines as these drugs transit from laboratory testing to studying its action, efficacy and safety in human patients. It is “the gateway between scientific research and clinical medicine”.<sup>(1)</sup> As newer treatment options are developed to address the rising need of treating medical diseases with better outcomes and safety, Phase I clinical trials become increasingly important to build the foundation of evidence required before it passes to expanded patient testing.

Therefore, to ensure that Malaysia is on par with countries that have long-standing and established practices in conducting Phase I trials, the Ministry of Health embarked on developing the Malaysian Phase I Clinical Trial Guidelines. These guidelines aim to be the standard reference for the conduct of first-in-human (FIH) trials in the country and are based on the well-recognised and established Association of British Pharmaceutical Industry Guidelines for the conduct of Phase I trials.

I would like to extend my appreciation and gratitude to the writing committee of this first edition guideline, which I am certain will prove to be invaluable to all stakeholders involved in the conduct of Phase I (including first-in-human) trials. My hope is that the implementation of these guidelines will pave the way to Malaysia emerging as a reliable, efficient and established Phase I clinical trial destination.

A handwritten signature in black ink, appearing to be 'S. Subramaniam', written over a light blue background.

**Datuk Seri Dr. S. Subramaniam**  
*Health Minister, Malaysia*





### **A message from the Director General of Health, Malaysia**

The development of Malaysia's first Phase I Clinical Trial Guideline marks an important milestone in the history of clinical research in Malaysia. This guideline is part of a much bigger initiative of the Phase I Realization Project (P1RP) that aims to build a complete and comprehensive early phase clinical research ecosystem in the country. Inpouring of early phase studies presents multiple socioeconomic advantages and these include transfer of knowledge and technologies, inflow of investments, better healthcare infrastructure and increased economic activity.

In a more local context, early phase studies play a key role in enhancing the capability of Malaysia in the development of medical science and treatment of diseases. It also helps our pharmaceutical industries gain first-hand experience in ensuring the efficacy and safety of their new drugs. Through the P1RP, a multi-pronged strategy has been developed to create the right ecosystem. Plans are already on the way to equip the regulatory agencies with the right knowledge to review Phase I studies that conform to international standards, setting up of a Scientific Review Panel to ensure the rights and safety of clinical trial participants and preparing the sites to conduct these studies.

I would like to take this opportunity to congratulate the steering committee members who have committed their time and contributed their knowledge to produce this guideline in a timely manner. I have no doubt that this guideline will provide useful guidance to sponsors, contract research organizations, investigators and clinical trial sites that wish to conduct early phase studies in Malaysia.

A handwritten signature in black ink, appearing to read 'Hisham'.

**Datuk Dr. Noor Hisham bin Abdullah**  
*Director General of Health, Malaysia*

## List of expert panel members (alphabetical order)

**Tan Sri Dato' Dr. Abu Bakar Suleiman**

*President,  
IMU Health*

**Prof. Dr. Abd Rashid Abd Rahman**

*Senior Consultant Physician,  
An Nur Specialist Hospital*

**Dr. Alan Fong Yean Yip**

*Consultant Cardiologist & Clinical Research Centre Head  
Sarawak General Hospital*

**Dr. Ami Fazlin Syed Mohamed**

*Head of Herbal Medicine Research Centre  
Institute for Medical Research*

**Dato' Dr. Chang Kian Meng**

*Consultant Haematologist, Ampang Hospital  
Chairman of Medical Research & Ethics Committee*

**Mr. Chew Chun Keat**

*Pharmacist, Clinical Trial Unit, Clinical Research Centre  
Hospital Ampang*

**Prof. Dr. Chim C Lang**

*Professor of Cardiology, Division of Molecular & Clinical Medicine,  
Medical Research Institute, Ninewells Hospital & Medical School, Dundee*

**Dr. Lee Ann Hodges**

*Senior Clinical Project Manager  
QuintilesIMS*

**Dr. Lee Toong Chow**

*Managing Director  
Info Kinetics Sdn Bhd*

**Dr. GR Letchuman Ramanathan**

*Senior Consultant Physician and Endocrinologist  
Hospital Raja Permaisuri Bainun*

**Dr. Linda B. Hakes**

*Chairman  
Academy of Pharmaceutical Sciences, UK*

**Prof Datuk Dr Looi Lai Meng**

*Senior Consultant Histopathologist,  
Department of Pathology, Faculty of Medicine, University of Malaya*

**Datuk Dr. Muhammad Radzi Abu Hassan**  
*Consultant Physician and Gastroenterologist*  
*Hospital Sultanah Bahiyah*

**Mr. Nicholas Leow Chun Wei**  
*Senior Principal Assistant Director*  
*Centre for Investigational New Product, National Pharmaceutical Regulatory Agency*

**Mdm Yam Pei Ching**  
*Principal Assistant Director*  
*Centre for Investigational New Product, National Pharmaceutical Regulatory Agency*

**Prof Datin Dr Zahurin bt Mohamed**  
*Professor*  
*Department of Pharmacology, Faculty of Medicine, University of Malaya*

# 1: Introduction

Clinical trials are a means by which new medicines or medical procedures are researched to ensure that they are efficacious and safe to be prescribed or applied to patients.<sup>(2)</sup> Clinical trials are categorised into 4 major phases, with Phase I trials focusing on the pharmacokinetics, safety, and effects on the body systems. Once the treatment passes the Phase I trial, Phase II trials are required to additionally look at the efficacy of the treatment in the patient population itself, whilst Phase III trials are conducted for the same purpose in a larger population of patients. Phase IV trials are considered post-marketing studies and are usually focused on the safety of marketed treatments.<sup>(2)</sup>

It takes an average of 11 years<sup>(3)</sup> before a drug can be registered for use in the market, and only about 60% of investigational products (IP) proceed from Phase I trials to Phase II trials. Out of this, only 11% are marketed.<sup>(1)</sup> With the aim of reducing the time taken for IPs to reach the market and to reduce the cost of development of new medicines, an additional form of Phase I trial was introduced by the United States Food and Drug Administration in 2004.<sup>(4)</sup> This was called exploratory first-in-human trials and was considered as “early Phase I trials”.

The shift of industry-sponsored clinical trials to regions like Asia has prompted the Malaysian government to target clinical research, particularly clinical trials, as one of its main economic growth factors.<sup>(5)</sup> The Malaysian Phase I Clinical Trial Guideline writing committee was therefore set up under the directive of the Malaysian Ministry of Health to develop a standard reference for the conduct of first-in-human (FIH) trials in the country. The committee members include experts in the field of clinical trials from the Ministry of Health, Ministry of Higher Education and Contract Research Organisations (CROs). In addition, international experts on clinical trials were also invited as Subject Matter Experts and to be part of the steering committee. This guideline was also distributed to the pharmaceutical industry (sponsors and CROs) for their feedback.

This guideline was developed based on the Association of British Pharmaceutical Industry Guidelines for the conduct of Phase I trials (2012 edition)<sup>(1)</sup>, wherein particular sections in the proceeding chapters have been reproduced from the document. Taking into consideration the local regulatory bodies and agencies’ existing procedures and the local clinical trial environment, adaptation of relevant areas has been done to facilitate the applicability of these guidelines in Malaysia.

The guidelines only give an overview of the conduct of Phase I (including FIH) trials in Malaysia. Professional interpretation of these guidelines based on current local existing acts and regulations is required, and proper judgment should be exercised in specific situations/clinical trials. Included in the appendices (Appendix 4) is a list of custodians. Sponsors of Phase I (including FIH) trials are strongly encouraged to seek out the relevant agencies to ensure that all processes are followed as per the most current requirements/regulations.

***Important note: As mentioned above, this guideline uses sections from the Association of British Pharmaceutical Industry Guidelines (APBI), either in part or whole, adapted to the Malaysian clinical trial environment or verbatim. The proceeding contents will therefore not cite the APBI in-text. However, the reader is encouraged to refer to the original source document.***

## 2: Developing a new medicine

Drug-related research is mainly sponsored by the pharmaceutical industry. A sponsor has to investigate and demonstrate a medicine's safety, quality and efficacy in a series of trials in humans before they obtain a licence for its manufacture and sales.

Before an IP can be given to humans, the sponsors must obtain certain information from studies carried out in animals. The main aims of these pre-clinical studies are (refer to Appendix 1):<sup>(6, 7)</sup>

- To investigate the effects of the drug on body systems – Pharmacodynamic (PD) studies<sup>(6)</sup>
- To investigate the blood levels of the drug and its absorption, distribution, metabolism and elimination after dosing – Pharmacokinetic (PK) studies<sup>(6)</sup>
- To calculate the dose range of the drug/IP and to identify the target organs and the margin of safety based on (a) the no-observed-adverse-effect dose level (NOAEL) relative to body weight and (b) drug exposure – the concentration of drug in the bloodstream over 24 hours -Toxicokinetic studies<sup>(7)</sup>

In addition, a formulation of the drug (IP), such as a capsule or injection, suitable for early studies in humans must be developed.

After the objectives of pre-clinical studies are met, trials are normally carried out in four phases. In practice, these trials may often overlap. A licence for marketing authorisation is granted after the first 3 phases are successfully carried out, while Phase IV is carried out after marketing authorisation of the drug is received. The phases of trials differ from each other in terms of the number and types of study subject, and the objective of the study:

Phase	Typical number and type of subject	Objective
1	50-200  Subjects are usually healthy volunteers or patients who are not expected to benefit from the IP.	1. Determination of safety of the IP in humans.  2. To determine the body's reaction to the IP (PK studies).  3. To determine the effect of the IP on the body (PD studies).  4. To determine if the IP works in patients (mainly relevant in Phase I oncology trials)  .
2	100-400  Subjects are patients with the targeted disease.	1. Determination of safety of IP in patients.  2. To determine the efficacy of the IP in patients.

3	1000-5000 Subjects are patients with the targeted disease. Number of subjects is greater than the Phase II trials.	1. Determination of safety of the IP in patients. 2. To confirm the efficacy of the IP in patients.
4.	Many thousands of patients with the targeted disease. Post marketing studies.	1. Pharmacovigilance surveillance studies. 2. Real world effectiveness of the medicine. 3. Comparison of new medicine against similar medicines.

The phases of trials are sometimes subdivided. For example, a trial with small-scale, exploratory efficacy studies in a limited number of patients may be referred to as ‘Phase IIa’, while slightly larger ‘dose-range finding’ trials carried out to find the efficacy of a compound at different doses might be referred to as ‘Phase IIb’.

It may take up to 11 years to successfully test an IP in Phases I to III.<sup>(3)</sup> IPs may be withdrawn from development for the following reasons:<sup>(8)</sup>

- IPs tested have been found not to be ‘well-tolerated’ or safe enough in humans
- IPs tested do not have a favourable PK or PD profile in humans
- IPs tested have been found to be insufficiently effective in patients with the target disease

A 10-year review of IPs showed that only 60% of the IPs progressed from Phase I to II, and only 11% were successfully marketed. The Phase I trials can identify IPs with potential for success as well as excluding failures thereby preventing unnecessary exposure of many more subjects to the IP.

In the past decade, exploratory studies have been carried out prior to Phase I single-dose escalation i.e., single dose given in increasing amounts. These studies expose a limited number of subjects to a much-reduced dose (*micro-dose*) of an IP.<sup>(4)</sup>

When the IP is already in a more advanced stage of development, a range of Phase I studies is performed. A Phase I study may be defined as a non-therapeutic, exploratory trial in human subjects who may be healthy or have a specific disease.<sup>(2)</sup> Unlike the later phase trials, the Phase I subjects usually do not get any therapeutic benefit from the trial.

The primary parameters for which the IP is tested at single/multiple doses in Phase I studies are:<sup>(2)</sup>

- Safety and tolerability
- PK
- PD

To address specific objectives regarding the IP, a range of distinct Phase I studies is designed as follows:

### **2.1. First-in-Human trial**

The first-in-human (FIH) trial of an IP is the first trial carried out in humans, usually a single dose escalation trial. These trials are carried out with the goals to assess the tolerability, safety, PK and, if possible, the PD effects of the IP. These trials also compare the results with those from the pre-clinical studies.

### **2.2. Subsequent trials**

Subsequent trials are usually required to investigate the effects of multiple ascending doses after the FIH trial.

Subsequent Phase I trials may be required to assess the following:

- The influence of the effects of potential factors such as food, gender, age and genetic differences, on the activity of the IP
- To investigate the impact of renal or hepatic insufficiency on the PK and safety of the IP
- The dose of IP vs. response relationship - by measuring biomarkers or using challenge agents
- Possible interactions of the IP with marketed medicines
- The absorption, distribution, metabolism and elimination by using a radiolabelled IP
- Bioavailability or bioequivalence of the IP
- The effect of the IP on the QT interval of the electrocardiogram (ECG)<sup>(9)</sup>

There is an increasing tendency for sponsors to combine the first single-dose and multiple-dose trials of an IP, and even add a trial of the effect of food or age, so that the FIH trial is merely the first of a 'bundle' of trials. Some of these trials, such as the interaction trials and QT-interval trial, may be done during any stage of development of an IP. While it is customary to refer to pharmacokinetic studies as 'Phase I', it is not very helpful and might lead to confusions.

### 3: Reviews and approvals in Phase I clinical trials

All planned Phase I trials including protocol amendments must be reviewed and where necessary must be approved by the relevant bodies as described below. The full process summary can be found in Appendix 2.

#### 3.1. National Pharmaceutical Regulatory Agency (NPR A)

The Phase I facility which will be conducting FIH and First Dose in Human studies must be accredited by the NPR A. Submission of the protocol for a FIH study to the NPR A and SRP can be done at the same time. NPR A will then issue a Clinical Trial Notification (CTN) while the Scientific Review Panel (SRP) will provide their opinion to the Ethics Committee. The sponsors may refer to the NPR A guidelines on the NPR A website (<http://npra.moh.gov.my>).<sup>(10)</sup>

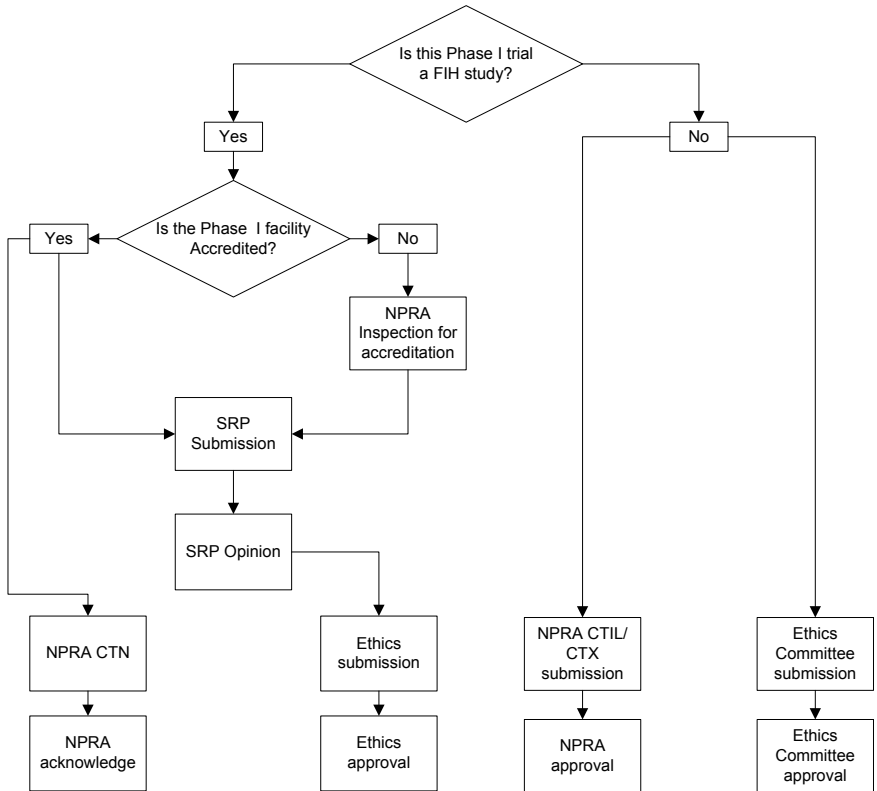


Figure 1: Application for Phase I clinical trials in Malaysia process flow.

FIH: First-in-human; CTN: Clinical Trial Notification; CTIL/CTX: Clinical Trial Import License/Clinical Trial Exemption (for manufacturing); SRP: Scientific Review Panel; NPR A: National Pharmaceutical Regulatory Agency. The full process summary, which also includes and pre- and post-application phases can be found in Appendix 2.



### 3.1.1. Certification of FIH facilities

All FIH units must be certified by the NPRA before they can be used for such studies. The NPRA inspections will be done in accordance to the applicable international standards and local regulatory requirements.<sup>(10)</sup>

Evidence of compliance to Good Manufacturing Practice (GMP) standards may be required by the NPRA in the event that manufacturing/compounding of the IP is done on site in accordance with the local regulatory requirements.<sup>(10)</sup>

### 3.2 Scientific Review Panel (SRP)

The SRP is a panel of expert reviewers appointed by the National Committee for Clinical Research (NCCR), Ministry of Health. The panel will include members from specialties related to the FIH trial disease/condition studied.

The sponsor of a FIH clinical trial must submit the full dossier to the SRP for review. This is to be done concurrently with submission to the **Institutional Review Board (IRB)/Independent Ethics Committee (IEC)** and notification to NPRA. Upon completion of the review, the SRP will inform the NPRA and IRB/IEC of its opinion. (Refer Figure 1)

### 3.3: Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before starting a Phase I trial in healthy subjects or in patients, the investigator must obtain written approval of an IRB/IEC registered with the Drug Control Authority (DCA).<sup>(10)</sup> It is recommended that these IRB/IECs have expertise and experience in reviewing Phase I trials.

Guidance on the process of applying for ethics approval, types of IRB/IECs, communication with IRB/IECs during a clinical trial, and protocol amendments can be found in the instructions/web sites provided by the relevant IRB/IECs.

<sup>1</sup>A list of DCA registered IRB/IECs is available on the website of NPRA (<http://npra.moh.gov.my>).<sup>(10)</sup>

## 4: Risk assessment

### 4.1. All investigational products (IPs)

The definition of an IP is “a pharmaceutical form of an active ingredient including herbal/ animal medicinal products or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use”<sup>(11)</sup>

In Phase I trials, the risk of harming the study volunteers should be minimal, as they get no therapeutic benefit from the IP. Before each trial, especially during the transition from pre-clinical studies to the FIH trial, the risk of tolerability and safety of IP must be fully assessed.

The sponsor must have the pre-clinical data reviewed by people who have the appropriate technical, scientific and clinical expertise. The project must have at least one independent reviewer.

External advisors can be used if sponsors do not have their own experts.

While evaluating the risk, all aspects of the IP – such as its class, novelty, species specificity, mode of action, potency, dose- and concentration-response relationship for efficacy and toxicity, and route of administration – must be taken into account.

Risk must be assessed on a case-by-case basis. The seriousness of possible adverse reactions and the probability of them happening must both be considered.

### 4.2. Higher risk IPs<sup>(6)</sup>

#### *Potential high-risk investigational products*

Medicinal products are defined as ‘potential high-risk medicinal products’ when there are concerns that serious adverse reactions may occur in FIH clinical trials that are related to either prior knowledge or the uncertain aspects of the products such as its mode of action, and/or the nature of the target, and/or the relevance of animal models.

Even though conventional non-clinical programmes provide an acceptable safety estimate for a first administration in humans for many new medicinal products, in the case of high-risk medicinal products these tests might not be sufficiently predictive of serious adverse reactions in man. Therefore, the development programme of high-risk investigational products might require special consideration when transitioning from non-clinical to clinical testing so as to minimise these risks.

When deciding the potential high-risk of these products, the following criteria should be taken into account on a case-by-case basis and the sponsor should discuss these in their clinical trial authorisation application.

#### ➤ *Mode of action*

Consideration should be given to the novelty, plausibility and extent of knowledge of the proposed mode of action, which include the nature, and intensity (extent, amplification, duration, reversibility) of the effect of the active substance on the target and the type of dose response (linear, non-linear, U-shaped, bell-shaped). Previous exposure of human subjects to compounds that have related biological mechanisms should also be considered. For example,

the following mechanisms could be considered as high risk:

- A pleiotropic mechanism, e.g. leading to various physiological effects, or targets that are ubiquitously expressed, as often seen in the immune system
- A mechanism that bypasses physiological control mechanisms, e.g. CD3 or CD28 (supra-) agonists.

The sponsors should also discuss the novelty of the structure of the medicinal product, even if the parent compounds are well established, for example a new type of engineered structural format like bi-specific antibodies or novel fusion proteins.

➤ *Nature of the target*

The nature of the target itself might impact the inherent risk to a first administration to humans regardless of the mode of action and sponsors should discuss the following aspects accordingly:

- The extent of the knowledge on the structure, tissue distribution, cell specificity, disease specificity, regulation, and biological function of the human target including “down-stream” effects.
- The relationship between the biology of the target, and the physiological or pharmacological effects, in both normal and pathological states.

➤ *Relevance of animal models*

The sponsor should take into account various aspects when comparing the available animal species to humans such as the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects. If available animal models are of limited relevance to study properly the pharmacological and toxicological effects of the medicinal product, it should be considered as high-risk.

### **4.3. Other factors**

The risk assessment must also take into account factors such as the procedures and any non-IP used in the trial, and whether the trial should be done in healthy subjects or patients.

## 5: Risk management

There must always be a strategy for ensuring minimal risk throughout the Phase I trial.

Should potential investigators be concerned about the level of risk of the IP, the sponsor must give them access to relevant people with responsibility for evaluating the pre-clinical work. There should be good liaison between the sponsor's physician and the investigator.

An independent advisor should be consulted if investigators still have concerns about pre-clinical data.

Assessment and management of risks should be well documented in a risk management plan. All aspects of the trial should be considered in the strategy for managing risk.

### 5.1. Starting dose

The starting dose of an IP should be a small fraction, preferably not more than 10% of the predicted therapeutic dose.

The FDA Guidance method of calculating the safe starting dose in man follows a stepwise process:<sup>(12)</sup>

- First, convert the 'no observed adverse effect level' (NOAEL) from the toxicology studies to a human equivalent dose (HED) on the basis of body surface area. The conversion factor is a unit-less number that converts mg/kg from animal species to the dose in humans.
- Then, select HED from the most appropriate species
- After that, apply a safety factor ( $\geq 10$ -fold) to give a maximum recommended starting dose (MRSD). This is obtained by dividing the HED by the safety factor generating the MRSD in mg/kg.
- Finally, adjust the MRSD on the basis of the predicted pharmacological action of the IP

This method is simple and supported by a wealth of historical evidence. Rather than selecting a dose with minimal pharmacological activity, the emphasis is on selecting a dose with minimal risk of toxicity based on the NOAEL, and its focus is on the dose of the IP rather than exposure.

The *European Medicines Agency (EMA) Guideline on strategies to identify and mitigate risks for FIH trials with IPs* recommends the use of a different approach to calculate a safe starting dose for high-risk agents, based on the minimal anticipated biological effect level (MABEL).<sup>(13)</sup> This approach uses all relevant information, taking into account: novelty; potency; mechanism of action; degree of species specificity; dose-response data from human and animal cells *in vitro*; dose- and concentration response data from animals *in vivo*; PK and PD modeling; calculated target occupancy versus concentration; and concentration of the target or target cells in humans *in vivo*.<sup>(13)</sup>

Doses calculated from different methods give different estimates. In such a case, the lowest value should be taken and a margin of safety built into the actual starting dose. The calculated starting dose should be reduced, if the pre-clinical data are likely to be a poor guide to responses in humans and if the dose-response curve is steep, the dose is increased in smaller increments.

## 5.2. Increasing the dose

In an ascending dose trial, the dose is often increased three- to five-fold at each increment at the lower doses and smaller increments around the expected therapeutic range. Increases in dose, and the amount of the increase, should be made only after carefully assessing all of the available data from previous doses. Serial measurements of the IP in blood during the trial allow increases in dose to be guided by exposure to the IP. As a general rule, the 'dose/toxicity or dose/effect relation observed in non-clinical studies, depending on which is steeper, should guide the dose increment between the two dose levels. The steeper the increase in the dose/toxicity or dose/effect curves, the lower the dose increment that should be selected.

Before deciding to increase the dose, the investigators, the sponsor's physician, and the sponsor's expert in PK, if appropriate, should review all of the available data including the pre-clinical data. Sponsors without a physician experienced in FIH studies should use an independent medical monitor. An intermediate dose should be given if there are any concerns about tolerability and safety of the IP or if exceeding the NOAEL, but only if the protocol allows. The basis of all decisions on increasing the dose must be documented.

## 5.3. Administration of doses

The number of subjects dosed on any one occasion, and the interval between dosing individual subjects and cohorts of subjects, will depend on the IP, its route of administration, and the type of trial. For example, only one subject should be given an active IP at the very first administration of a high-risk IP. And if the route of administration is intravenous, the dose should be given by slow infusion, perhaps over several hours, rather than by rapid injection, unless there is a good reason for that method. The protocol should include details for the rate and duration of infusion. In contrast, if the IP is of low risk and the route of administration is oral, cohorts of subjects can be dosed on the same occasion, and at short intervals e.g. 5 to 10 minutes.

## 5.4. Facilities and staff

FIH trials of an IP are regarded as higher risk than other Phase I trials. However, the risk during transition from pre-clinical studies to the very first-human-trial may be no higher than it is during other transition trials, such as from single to multiple doses, from young to elderly subjects, and from administration of the IP alone to giving it with established medicines during interaction trials. The sponsors must place their trials of an IP, especially FIH trial and other transition trials, with Phase I units, including their own, whose staff, premises and facilities match the level of risk of the IP. Furthermore, investigators must not take on trials of an IP for which they do not have adequate experience or training.

The investigator must assess the risk of harm, by reviewing the protocol, investigator's brochure, IP dossier and, as required by the Declaration of Helsinki, any relevant medical and scientific literature. In addition, the investigator must weigh the foreseeable risks and inconveniences against the expected benefits for the individual subject, and for future subjects with the target disease. Finally, the investigator must explain and justify any risks in the informed consent form for trial subjects and in the IRB/IEC application.

All accredited units are expected to have the following:<sup>(14)</sup>

1. It is expected that the unit has either an existing agreement with the hospital for supporting emergencies arising from their clinical trials or is able to demonstrate communication and notification of trial information (e.g. dosing times) with the hospital's emergency teams. The hospital emergency response team and the Intensive Treatment Unit (ITU) must be aware of the Research Unit, the nature of the research (e.g. FIH, biologicals), and that patients could be referred to them from the unit at any time.
2. The accredited unit must have robust (and tested) arrangements for immediate maintenance of life support (i.e. resuscitation and stabilisation) and onward transfer of subjects to hospital, where necessary. Periodic testing of emergency scenarios should occur within the unit, according to local requirements, and be documented.
3. There must be documentation that demonstrates that physicians are authorised to act as principal investigators in FIH studies, as described by their job description, and supported by a *curriculum vitae* and training records. It is expected that Principal Investigators have relevant clinical experience and will ensure that the study team has expertise related to FIH trials that includes relevant qualifications in Pharmaceutical Medicine, Human Pharmacology, Clinical Pharmacology or equivalent.
4. The accredited unit must have appropriate numbers of staff with adequate training to handle medical emergencies.
5. Contracts and agreements with sponsors (or internal memorandum of understanding for in-house units) must detail procedures and responsibilities for notifying the investigator immediately if/when new safety/toxicology data come to light.
6. There must be a procedure in place to address 'over volunteering' (refer Sections 9.1 and 9.2).
7. There must be written Standard Operating Procedures (SOPs) for every aspect of the study process. Specifically, these SOPs must include:
  - Transfer of subjects to hospital; to include the provision of all relevant medical information regarding the trial and the subject(s) in question to the hospital
  - Medical emergencies to include stabilising subjects in an acute emergency
  - Out-of-hours medical cover and contact with sponsor or IP responsible person(s)
  - Training and refresher training in emergency resuscitation procedures
  - Procedures for handling common medical emergencies e.g. syncope, hypotension, anaphylaxis, cardiac arrest
  - Unblinding in an emergency
  - Dose escalation

8. The unit must be able to demonstrate that there are sufficient numbers of trained staff employed by or contracted to the unit. 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.
9. Clinical staff must be appropriately and currently trained to initiate resuscitation i.e. basic airway management and ventilation, IV cannulation and fluid therapy, giving adrenaline, cardiopulmonary resuscitation (CPR) and use of an automated external defibrillator (AED). At a minimum clinical staff should receive Basic Life Support (BLS) training. Annual updates such as refresher training are required.
10. An emergency trolley should be available that is easily and rapidly accessible. There should be a trolley in each main area that can be moved quickly to where it is needed. The emergency trolley should carry as a minimum:
  - Oxygen and delivery apparatus
  - Equipment for procedures such as cannulation and suitable fluids for IV infusion
  - Laryngeal Mask Airways or other supraglottic airway devices
  - Self-inflating bag, or equivalent, for assisted ventilation
  - Suction equipment
  - Defibrillator – this should be an AED with a manual override
  - Instruments for intubation and emergency cricothyroidotomy should be carried on the trolley for use by appropriately experienced personnel or a responding emergency team only.
11. Continuous monitoring equipment must be available to include ECG, pulse oximetry, vital signs such as blood pressure, heart rate, temperature and respiratory rate.
12. The contents of the trolley should be checked weekly and the checks documented. Expiry dates for medication on the trolley should be checked regularly and documented. If the trolley or the emergency drug box is sealed then the tamper proof seal should be checked weekly.
13. Subjects must be provided with 24-hour emergency contact numbers for while they are outside the unit. The Unit must also hold the contact numbers for volunteers to ensure that they can be contacted outside the unit should the need arise.
14. Beds (where used for dosing days) must be able to be tilted and adjusted for height.
15. There must be alarm points in areas where the subjects will be e.g. showers, toilets, in the ward and recreational area. Staff must be able to open bathroom doors from the outside in an emergency.
16. There must be a robust procedure in place to accurately identify subjects such as utilising photographic identification, to ensure that the person screened is the person dosed.

## 5.5. Procedures

Non-invasive trial procedures should be used whenever possible. If invasive procedures such as an arterial cannula, a biopsy or an endoscopy are used, they must be done or supervised by someone skilled in the procedure.

## 5.6. Subjects

The decision as to whether a Phase I trial should be conducted in healthy subjects or patients should be made on a case-by-case basis. Compared with patients, healthy subjects are easier to find, more robust, free of other medicines, more likely to respond uniformly, and better at completing long and complex trials. Typically, healthy subjects tolerate IPs better than patients. On the other hand, for some IPs, obese subjects or subjects with high serum cholesterol may be more suitable than truly healthy subjects. IPs classified as “high-risk” such as cancer treatment or gene therapy should be tested on patients with the target disease. Other than the PK and/or PD findings in healthy subjects not having an accurate predictive value compared to those with the disease, the risk of toxicity in healthy subjects may outweigh the justification of including them.



## 6: Safety record of Phase I trials

Phase I trials have a good safety record in reviews that have focused on safety.<sup>(15)</sup> However, it has been documented that healthy subjects have also died during these trials. For example, a Phase I trial conducted by Biotrial on BIA 10-2474, an analgesic acting on cannabinoid receptors, was stopped after a healthy volunteer was declared brain-dead, while other volunteers suffered serious neurological damage.<sup>(16)</sup>

As IPs have the potential to harm subjects in Phase I trials, it is important to:

- Thoroughly review and document subjects' medical history
- Keep subjects overnight in line with risk assessment/study design
- Review all the relevant scientific and medical literature before starting a clinical trial (refer Appendix 3)

At one time, almost all IPs were new chemical entities (NCE). Now, many are biological in nature. Many biological IPs – such as proteins, cytokines, and monoclonal antibodies – have been tested safely in FIH trials in healthy subjects or in patients. However, compared with NCE, there is a paucity of data about their overall safety. Some reasons why biological IPs, especially monoclonal antibodies, should be seen as different from NCE are:

- Proteins can cause anaphylactic or infusion reactions
- Even a single dose of a fully humanised protein can induce an immune response
- There is a report of a delayed hypersensitivity reaction to re-challenge with a monoclonal antibody after a long period of non-exposure
- Two monoclonal antibodies in clinical use have caused progressive multifocal leukoencephalopathy (PML), a rare and usually fatal infection of the brain and spinal cord due to reactivation of a virus (JC polyoma) which most people carry
- TGN1412 – a monoclonal antibody that differs from those in clinical use in that it activates rather than blocks an immune response – caused a 'cytokine storm' and organ failure in all six previously healthy subjects who received it in a FIH trial

If the risk of giving a biological IP to healthy subjects is more than minimal, patients with the target disease might be studied instead. However, the substitution of patients for healthy volunteers must be carefully considered, especially if no potential benefit is expected to arise from participation in the study. Their condition might make patients more susceptible or less tolerant to unwanted effects from the investigational product. Also, the mass of tissue being targeted by the IP may be much increased in patients compared with healthy subjects. A careful risk/benefit analysis should be performed before deciding on the appropriate study population. Properly validated biomarkers may help monitor potential risks.

## 7: Protocol and Investigator’s Brochure (IB)

A clinical trial must be scientifically sound and described in a clear, detailed protocol, supplemented with a detailed IB. The protocol and IB for a Phase I trial should emphasise:

- The pre-clinical information – such as pharmacology and toxicology of the IP. For more details, please refer to Appendix 1 and Section 4.3 of EMA guideline on ***Strategies to identify and mitigate risks for FIH clinical trials with investigational products, 2016***.<sup>(13)</sup>
- The assessment of risk of harm from the IP, trial procedures and any non-IP
- The justification of that assessment, and how the risk will be kept minimal throughout the trial
- The methods of deciding: the first dose; the maximum dose; the increases in dose; the route of administration; the rate of administration of intravenous doses; the interval between dosing individual subjects; and the number of subjects to be dosed on any one occasion; the minimum set of data or subject numbers required for decision-making
- Any assessment of dose- or concentration-response relationships
- Any pharmacy work needed to prepare doses of the IP for administration
- Stopping or withdrawal criteria.

For detailed information on protocol contents, please refer to Section 8.2 of EMA guideline on ***Strategies to identify and mitigate risks for FIH clinical trials with investigational products, 2016***.<sup>(13)</sup>

Many Phase I trials, especially the early ones, cannot be completed without protocol amendments. There are three types – substantial, urgent and minor. An amendment is substantial if it is likely to have a significant impact on:

- The safety or physical or mental integrity of the trial subjects
- The scientific value of the trial
- The conduct or management of the trial, or
- The quality or safety of any IP used in the trial

The sponsor decides whether an amendment is substantial. If the amendment is deemed substantial an approval from the IRB/IEC should be sought. The investigator and sponsor may implement a substantial amendment without IRB/IEC and NPRA approval, respectively, if the change is an urgent safety measure to protect the trial subjects. However, the investigator and sponsor must notify the IRB/IEC within 24 hours afterwards and expedite a written report to NPRA.<sup>(10)</sup> All SAEs in FIH studies must be reported to NPRA and the IRB/IEC.

In order to cope with unexpected findings, and to prevent the need for protocol amendments, an appropriate degree of flexibility should be built into the protocol. For example, there should be scope to modify dose increments and frequency of blood sampling as safety and pharmacokinetic data become available. Additionally, the investigators should be able to use their clinical judgment to allow inclusion of subjects with minor out-of-range results of screening tests of blood and urine, and minor variants of the ECG.

## 8: Contracts

When entering into an agreement to conduct a trial, the sponsor must provide the investigator with copies of the protocol, up-to-date investigator's brochure, investigational product (IP) dossier, CTIL/CTX application and approval letter, indemnity, and insurance, all of which the investigator must review.

If the investigator agrees to perform the trial, there must be a written, dated and signed trial-specific contract between the sponsor, institution and the investigator, and between the investigator/institution and any subcontractors, which sets out the obligations of the parties for trial-related tasks and for financial matters. Examples of subcontractors are a laboratory and a commercial archivist. The protocol may serve as the basis of a contract. In order to protect the clinical trial investigators and the trial subjects, contracts must be in place before the start of the trial.

The contract should state the following:

- Start the trial only after it has undergone appropriate reviews and approvals (refer Section 2.0)
- Start and complete the trial in realistic times
- Undertake all the trial-related duties and functions allocated by the sponsor to the investigator
- Carry out the trial according to GCP, GMP, all relevant regulatory requirements, and the protocol
- Comply with procedures for recording or reporting data
- Allow direct access, by the sponsor's monitors and auditors, and by the NPRA and IRB/IEC, to the trial site, and to source documents, source data, and reports
- Confidentiality, publication policy, payments, reasons for non-payment, stopping the trial, storing and destroying trial-related documents, details of any equipment provided by the sponsor, and ownership of trial materials, records and results
- The sponsor abiding by recommendation on compensation for injury to trial subjects and indemnity for the investigator

The sponsor may transfer any or all of their trial-related duties and functions to a contract research organisation (CRO). The CRO must have sound finances, so that they can meet their contractual obligations. In this guideline, what applies to the sponsor may also apply to a CRO. However, the sponsor retains overall responsibility for the trial.<sup>9</sup>

## 9: Trial subjects

### 9.1. Recruitment

Potential trial subjects may be recruited:

- From a paper or electronic database of people who have indicated their willingness to take part in a trial
- By advertisements in a newspaper or magazine, or on a noticeboard in places such as a university or hospital, or on the radio or television, or on a website or any other social media platform
- By word of mouth
- By referral from another doctor

All study-specific advertisements must be approved by the relevant IRB/IEC.

Advertisements should say that the trial involves research and that the advertisement has been approved by an IRB/IEC, and should give a contact name and phone number and some of the selection criteria. In addition, advertisements may give the purpose of the trial, where it will take place and the name of the company or institution carrying it out. However, advertisements must never over-stress payment, use IRB/IEC approval as an inducement, name and promote the product, or claim that it is safe.

An ethics committee should review general advertising and screening procedures. General screening constitutes non-invasive procedures that are undertaken to evaluate a subject's eligibility to join a trial unit's volunteer panel. The creation and maintenance of such a database should comply with the Personal Data Protection Act.<sup>(17)</sup>

Subjects must be recruited of their own free will irrespective of the method used for recruitment. They should not be made to feel obliged to take part in a trial, nor should they suffer in any way if they do not take part. Additionally, they should be recruited only if they:

- Are capable of giving valid consent
- Have been fully and properly informed so that they understand:
  - The nature and purpose of the trial
  - Any risks, either known or suspected, and any inconvenience, discomfort or pain that they are likely to experience
  - That they can withdraw at any time and without giving a reason
  - That the investigator may withdraw them at any time if they do not follow the protocol or if their health is at risk

All units must keep records of subjects who take part in their trials and avoid excessive use of any subject. The number of trials that a subject may take part in during any 12-month period will depend on:

- The types of IP and their half-lives
- The routes of administration of the IP
- The frequency and duration of exposure to the IP
- The procedures involved
- The total volume of blood taken from the subject

Subjects must not:

- Take part in more than one trial at a time
- Receive more than 10 milliSieverts of radioactivity in any 12-month period

In general, subjects should not receive an IP systemically less than three months after the previous one.

## **9.2. Monitoring overexposure**

Trial subjects must provide proof of identity (e.g. identity card, passport or biometrics) before they take part in a trial and must be monitored and prevented from taking part in too many trials. The ways to ensure this are:

- Counselling the subject
- Including warnings in the information leaflet and consent form
- Units keeping a register of their clinical trials and subjects who have taken part in them – keeping photographic evidence of a subject's identity should be considered
- Contacting the subject's personal doctor
- Being vigilant when screening trial subjects, e.g. look for evidence, such as needle marks on the forearm and low blood counts, that the subject may have taken part in a trial recently
- Using an internet-based central register

The sponsor must include information about procedures for checking simultaneous or recent involvement of potential subjects in other trials in their submissions for approval.

## **9.3. Special populations**

### **9.3.1. Women**

A woman capable of having a child should take part in a trial of an IP only if:

- The reproductive toxicology studies have been completed and the results raise no concern against participation in clinical trials or there is a good reason why reproductive toxicology studies are not needed
- She is not pregnant, according to her menstrual history and a pregnancy test
- She will not be at risk of becoming pregnant during and for a specified interval after the trial
- She is warned about the potential risks to the developing child should she become pregnant
- She is tested for pregnancy during the trial, as appropriate

Women using a hormonal contraceptive, such as 'the pill', should use an alternative method of contraception until the possibility of an interaction with the IP has been excluded.

### **9.3.2. Children**

In the Malaysian context, FIH studies in children are not allowed by the NPRA. Other types of Phase I studies such as PK studies to establish suitability for paediatric use are subjected to the normal route of submission discussed in the guideline.

### **9.3.3. Elderly**

Trials of IPs in elderly subjects are justified if the product is intended for use in the elderly, and especially if its effects and metabolism might differ from those in younger subjects.

### **9.3.4. Vulnerable subjects**

Investigators must be wary of recruiting vulnerable trial subjects, such as the homeless, or employees of the company or students of the institution that is sponsoring or carrying out the trial.<sup>9</sup> Employees and students are, or may feel, vulnerable to pressure from someone who can influence their careers. Should such subjects decide to take part in the trial, they must be dealt with like other subjects in the trial, and not be allowed to let their normal work interfere with the trial. The investigator should forewarn employees, in a written agreement, of the possible implications of having their personal data processed at work by their colleagues. Employees and students may need to get permission from their employer or institution beforehand. Some sponsors bar use of employees from trials of IPs.

### **9.3.5. Patients**

All non-therapeutic trials of IPs – whether they involve healthy subjects or patients – are now called Phase I trials. The following are examples of Phase I trials involving patients.

- Subjects who are well but have a chronic, stable condition – such as asthma, type 2 diabetes or hypertension – may be given single doses or short courses of an IP from which they do not benefit therapeutically. Such trials, especially if they include a challenge agent, can help decide whether or not to proceed to trials in larger numbers of patients, who may benefit therapeutically.
- The FIH trial of a cytotoxic IP to treat cancer is usually a single ascending dose study, to assess the PK of the IP. Such trials have to be done in patients.
- Trials on the PK of an IP in patients with varying degrees of impaired kidney or liver function, in order to recommend adjustments to the dose in such patients, if appropriate. Such trials are difficult to do because of slow patient recruitment and ethical concerns. For these reasons, they are usually done late in the development of the IP.

### **9.4. Payments**

Many trials are demanding of the subject and involve long periods of residence in the study centre, many visits to the trial site, urine collections, multiple blood tests and other procedures that cause discomfort, as well as lifestyle restrictions. It is therefore right to pay subjects (healthy subjects and patients) who volunteer for Phase I trials more than just any expenses that they incur. The amount should be related to the duration of residence in the unit, the number and length of visits, lifestyle restrictions, and the type and extent of the inconvenience and discomfort involved. As a guide, payments should be based on the minimum hourly wage and should be increased for procedures requiring extra care on the part of the subject or involving more discomfort. Payment must never be related to risk.

Subjects who withdraw or are withdrawn even for medical reasons should be paid pro-rata depending on their level of involvement and adherence to the protocol. The investigator should decide the amount of payment depending on the circumstances. Payment may be reduced, if a subject does not follow the protocol, or may be increased, if the protocol is amended to allow further tests or visits.

If a trial is postponed or cancelled, subjects may be paid for setting aside time to do the trial. Reserve subjects, who 'stand by' in case someone drops out or are withdrawn from the trial before first dosing, should be paid.

The policy on paying trial subjects, and the amount, must be stated in the subject information leaflet and be approved by the IRB/IEC.



## 9.5. Obtaining informed consent

The investigator or delegate must:

- Obtain the consent of subjects only after the IRB/IEC has approved in writing the information and consent form
- Fully inform potential trial subjects before they agree to take part in the trial
- Give the subjects oral and written information that is free of jargon and is easy to understand
- Give the subjects enough time and opportunity to ask questions about the trial, answer their questions accurately and honestly, and ensure that they understand the answers
- Ensure that neither the investigator nor other staff coerce subjects to take part or continue to take part in the trial
- Give the subjects, in writing and after approval of the IRB/IEC, any new information that might make them change their mind about taking part in the trial
- Ensure that the subjects, and who informs them, sign and date a consent form, and are given a copy.

## 9.6. Screening

The investigator should judge trial subjects suitable on the basis of tests<sup>9</sup>, such as:

- A medical history and examination
- Medicines taken within a set period before the start of the trial
- A 12-lead ECG
- Routine safety tests of blood and urine
- Tests for relevant drugs of abuse e.g. alcohol, cannabinoids, cocaine, morphine, benzodiazepines, barbiturates and amphetamines
- Tests for HIV, hepatitis B and hepatitis C
- Pregnancy tests in women capable of having a child and at risk of becoming pregnant
- Trial-specific tests, such as 24-hour ambulatory ECG, echocardiogram, lung function tests, kidney function tests and genetic tests
- For IPs that affect the immune system: tests to exclude active or recent infections, such as tuberculosis and genitourinary infection, and willingness not to travel to countries for which vaccinations are intended or that present a higher risk of infectious diseases during the period that the IP may be active
- Information from personal doctor

Before subjects decide to have the tests for viruses and for drugs of abuse, the investigator must explain to them what will happen if one of the tests turns out to be positive.<sup>9</sup>

Healthy subjects often have minor out-of-range results of safety tests of blood and urine, and minor variants of the ECG. For example, serum transaminases that are out-of-range, red blood cells in the urine, and nodal rhythm of the ECG are common findings. Some monitors and auditors regard these as deviations from the protocol of a trial in healthy subjects. However, usually they have no clinical relevance and do not justify excluding subjects from a trial. A physician should decide their clinical relevance, and the protocol should allow for use of clinical judgement. If subjects are deemed unsuitable for a trial, they should be told why.

Investigators should ask potential trial subjects if they have taken part in a study in previous months. In addition, they should look for evidence, such as needle marks on the forearm and low blood counts, that the subject may have taken part in a trial recently.

## 9.7. Timing of recruitment and screening

### 9.7.1. Panel:

Investigators can recruit and screen subjects at any time for a panel of subjects interested in taking part in a Phase I trial, providing the IRB/IEC has given written approval of the 'screening' protocol and the subjects have given written consent.

### **9.7.2. Specific trial:**

Investigators can start to recruit subjects for a specific trial after the IRB/IEC has given written approval. However, investigators must not screen subjects for a specific trial before obtaining written approval of both the IRB/IEC and NPRA, and of course the subjects.<sup>(10)</sup>

If the investigator has IRB/IEC approval for panel recruitment and screening, and if the sponsor agrees, the investigator may transfer subjects and their data from a panel to a specific trial.<sup>(10)</sup> Before transferring subjects, investigators must not carry out procedures that are not covered by the protocol for panel recruitment and screening.

### **9.8. Identification**

Subjects who are judged suitable at screening must be either photographed or have some biometric identity check at subsequent visits to the unit. Subjects who are resident in the Phase I unit should be fitted with some form of identification, such as a wristband, with the subject's number and trial code. The subject's identity must be checked before carrying out procedures, such as taking blood samples, giving the trial IP, or recording information in the case report form (CRF). The subject's number or barcode should be used on all samples and results.

### **9.9. Informing the subject's personal doctor**

If applicable to the protocol, the investigator should ask potential trial subjects for permission to contact their personal doctor in order to obtain background health information.

The investigator should inform the personal doctor that their patient has agreed to take part in a trial and should ask if their patient:

- Has or had any relevant illnesses
- Is taking or has recently taken any medicines
- Has taken part in another clinical trial recently

The investigator should ask the personal doctor to reply in writing and may offer them payment for responding. The investigator must be able to justify including in the trial a subject whose personal doctor does not give any information. Whether or not the personal doctor responds, the investigator is ultimately responsible for making sure that subjects are suitable for the trial before allowing them to take part in it.

### **9.10. Safety**

The investigator must assess the health of trial subjects throughout the trial and should withdraw any subject whose health is at risk. The methods, which should be described in the protocol, include:

- Asking subjects about adverse events
- Medical examinations
- Measuring vital signs such as heart rate and blood pressure

- Routine safety tests of blood and urine
- Continuous monitoring of variables such as the ECG and pulse oximetry
- Trial-specific tests, such as lung function tests
- Requesting subjects' permission to access medical records

### **9.11. Follow-up**

The investigator must follow up:

- All subjects after their last dose of IP, for a period depending on the IP and the trial
- Subjects with adverse events, including clinically-relevant abnormal laboratory results, until they have resolved or it is clear that they are resolving
- Subjects who withdraw or are withdrawn from a trial, as if they had completed it, providing they agree

# 10: Pharmacy

## 10.1. Premises, facilities and equipment

All units should have a designated pharmacy area that is secure and accessible only to certain staff. The type of premises, facilities and equipment should reflect the types of trial that the investigator does for sponsors. For example, the investigator for a trial of an investigational product (IP) that is packed and labelled ready for administration to individual subjects will need only basic facilities to store and dispense the IP, and procedures to keep records of its receipt, use, retrieval and disposal. However, an investigator who assumes some or all of the sponsor's responsibilities for an IP will need to have the right premises, facilities, equipment and procedures, such as:

- Premises that are purpose-built or adapted for the purpose
- The right environment, such as directional air-flow that is controlled for particles, microbiological contamination and temperature, and is monitored appropriately
- A designated storage area, with a quarantine area, for the IP
- The right equipment, such as a laminar flow cabinet to prepare sterile products
- A rigorous quality management system
- A CTIL (Clinical Trial Import Licence)/CTX (Clinical Trial Exemption) to manufacture/ other regulatory requirements for IP, or to assemble IPs, including placebo and other comparators (refer Chapter 3)<sup>(10)</sup>
- Compliance to GMP requirement by NPRA or other relevant regulatory requirements.<sup>(10)</sup>

## 10.2. Storage

IPs should be stored in designated areas under conditions and for times recommended by the sponsor. Storage areas should:

- Have adequate space for different IPs to be stored apart
- Be temperature-controlled and humidity-monitored, with alarm controls
- Be protected from direct sunlight
- Be mapped to identify, and avoid using, hot and cold spots, if appropriate
- Be secure
- Be accessible only to authorised staff
- Have records for logging IPs in and out

The pharmacy should keep a stock of marketed medicines for managing common adverse events –

such as headache and nausea – and for managing medical emergencies other than cardiopulmonary resuscitation – such as convulsions and low blood sugar.

The sponsor should indicate whether an antidote to the IP exists and ensure its supply. These medicines must be readily available to clinical staff. If applicable, the necessary licenses must be obtained for these medicines.

### **10.3. Staff**

The pharmacy staff must be suitably qualified and experienced, and sufficient in number for the type and amount of work that the pharmacy undertakes.

A registered pharmacist, ideally with manufacturing experience, should prepare or assemble the IP. A pharmacist may delegate work to pharmacy technicians or assistants, but must supervise their work.

A physician or a pharmacist should have overall responsibility for IPs and marketed medicines, including emergency medicines.

Facilities authorised to manufacture IPs should allow regulators to inspect the premises at any reasonable time.

### **10.4. Types of work**

The work that the pharmacy might undertake, and for which GCP and GMP set the standards include: importing, packaging and labelling, randomisation, manufacture and batch release. The manufacture and batch release assessments will be covered during the GMP compliance assessment.

# 11: Investigational products

## 11.1. Manufacture

Whoever imports, manufactures, assembles or repackages IPs must apply for CTIL/CTX from NPRA (excluding FIH studies) and must comply with GMP.<sup>(10)</sup> Some examples of GMP activities are:

- Re-packing bulk capsules or tablets into unit-dose containers, and randomising and labelling them
- Weighing bulk material directly into capsules
- Preparing, under aseptic conditions, a formulation for parenteral use
- Receiving labelled unit-dose containers from another country

During the early stages of development of an IP, the manufacturing process may change as the sponsor learns more about the product. The sponsor's early formulations of an IP may be primitive and require finishing work by the Phase I unit before they are ready for administration to the trial subjects.

## 11.2. Documents

Pharmacies that manufacture or prepare IPs must have written instructions and records for their manufacturing processes. It should be possible to trace the history of each batch and any changes introduced during IP development.

## 11.3. Records

The pharmacy should keep records of manufacture, preparation, packaging, quality control, batch release, storage conditions, and shipping of an IP.

## 11.4. Supplying the investigator

The sponsor should not supply the investigator with an IP before:

- The CTIL/CTX or Clinical Trial Notification is obtained in writing
- The IRB/IEC application is approved in writing
- The IP has been certified by the sponsor
- The code-break is in place
- The clinical trial agreement between sponsor and investigator is in place

However, the sponsor may release the IP to responsible personnel of the Phase I unit, providing he or she quarantines it until the above conditions have been met.

### **11.5. Transport to the trial site**

The sponsor should pack the IP properly and ensure that storage requirements are met during transport to the investigator. Temperature loggers should be added to the container during the IP transportation.

### **11.6. Accountability at the trial site**

The investigator, pharmacist or other delegate should keep records of each stage of the handling and use of an IP, such as:

- Receiving it and assessing its condition on arrival, and notifying the findings to the sponsor
- Repackaging, relabelling, dispensing or manufacturing it
- Giving each subject the dose or doses specified by the protocol
- Returning unused product to the sponsor or delegate, or destroying it, as instructed by the sponsor
- Keeping an inventory
- Reconciling all the IP received from the sponsor

These records should include the dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the IP and to the trial subjects.

### **11.7. Recall**

The unit must have a system for retrieving the IP promptly at any time.

### **11.8. Randomisation**

There should be written procedures as appropriate for generation, distribution, handling and retention of any randomisation code used for packaging an IP.

### **11.9. Emergency unblinding**

The investigator or delegate must have a written procedure for rapidly identifying a 'blinded' IP in an emergency. The procedure must be secure, readily available at all times during the trial, and not allow breaks of the blinding to go undetected.



### **11.10. Quality management**

Manufacturing and dispensing IPs is more complex than manufacturing and dispensing marketed products due to:

- Production processes that are often not validated
- The lack of fixed routines
- The increased risk of contamination, including cross-contamination
- The need for blinding and randomisation in most trials

Therefore, units must have robust quality control and quality assurance procedures for manufacturing and dispensing IPs. The people responsible for manufacturing and dispensing should be independent of those responsible for quality management.

## 12: Management or handling of IP

### 12.1. Requirements

An importer of the IP must possess the appropriate regulatory approval on which a license holder is named.<sup>(10)</sup>

Phase I units with a pharmacy that dispenses, compounds/manufactures, or assembles IPs, including placebo and comparators, must have designated and responsible personnel for these activities.

Manufacturing of IPs on site shall be done in accordance with Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP requirements.<sup>(18)</sup> To ensure that IPs meet these requirements, the responsible person should have the following qualifications/criteria:

Pharmacist with:

- Poison Licence Type A/Annual Practising Certificate (APC)
- GMP trained
- GCP trained
- Manufacturing experience
- Job description that accurately reflects the duties

### 12.2. Responsibilities

Responsibilities of a licence holder are defined in Malaysian Guideline for Application of CTIL and CTX.<sup>(10)</sup>

The responsible person at the site must ensure that there are procedures in place to assure quality of IP and to retain all relevant and appropriate documentation.

### 12.3. Releasing IP prepared by the pharmacy

It is the role of the responsible person to release batches of IP. The site usually prepares an IP for small groups of subjects or just one subject at a time. The time between preparing the IP and giving it to the trial subjects may be a few hours or even minutes. It is not practical to have a responsible person available at all times. Therefore, units should devise a written procedure for releasing IP and be prepared to justify it during inspection for an IP. The responsible person may under some circumstances have to release some batches retrospectively. This should happen only on exception and identified in the CTX application.

When deciding whether to accept an IP prepared in the pharmacy for use in a clinical trial, the

responsible person should take into account, as appropriate:

- Randomisation code
- Protocol and amendments
- Pharmacy instructions
- Pharmacy SOP
- Details of any deviations from procedures and action taken
- Production records
- Results of QC testing
- Certificate of analysis
- Certificate of compliance with GMP
- Stability data
- Inspection of finished product
- Environmental monitoring records
- Validation, calibration, servicing and maintenance records
- Findings of any audits
- IP accountability and storage records

## 13: Resuscitation procedures, equipment, medicines and training

There must be procedures, equipment, medicines and trained staff to deal with any medical emergency that might arise during a trial, as follows.

### 13.1. General procedures

Trial subjects must:

- Have a call button by their bed and in places such as toilets and showers, to call trial staff
- Be given the information and consent form and an appointment card with the names and telephone numbers of the trial physicians, so that the subject (or another doctor who might see the subject) can call the 'on-call' physician or a trial physician at any time

Trial staff must have access to:

- Immediate medical cover throughout the trial
- An 'on-call' investigator or research personnel who can be contacted by telephone at any time
- The sponsor's medical monitor or defined delegates whom they can contact by telephone at any time. A cascade of contactable personnel on the sponsor's side should be available to the investigator site – this can be added to the study protocol or be detailed in a separate document
- A procedure to report serious adverse events
- The randomisation code, should a subject have a serious adverse event
- An alarm system, to call for assistance in case of a medical emergency
- Continuous monitoring of vital signs, such as ECG and pulse oximetry
- Procedures for dealing with the most likely medical emergencies, such as profound syncope, hypotension, anaphylaxis and cardiopulmonary arrest
- A procedure to transfer a trial subject to hospital (see below)
- Intensive care unit (immediate access is a pre-requisite in a FIH study)

### 13.2. Resuscitation equipment and medicines<sup>(14)</sup>

Refer to Section 5.4

### **13.3. Antidote**

If there is an antidote to the IP being tested, it must be readily available at all times. The same applies to non-IPs.

### **13.4. Resuscitation training**

Physicians, nurses and other staff who help to care for trial subjects must all be trained and hold a valid certificate in basic (BLS), or advanced life support (ALS) procedures, as appropriate. For example, all physicians must be trained and hold a valid certificate in ALS.

The medical director or another doctor with clinical expertise in resuscitation should set and maintain standards of training and assessment of the unit's staff, and ensure that competence is maintained by regular refresher training. Appropriately trained people, such as doctors and resuscitation training officers, should do the training and assessment.

# 14: Confidentiality

## 14.1. Sponsors

Sponsors expect investigators/institutions to keep confidential any commercially sensitive information, such as the protocol, investigator's brochure, IP dossier, and CRF. Trial subjects who ask to see the protocol should be allowed to do so, but not be allowed to keep a copy.

A statement about confidentiality is normally included in the trial protocol or contract. When trial-related documents are not in use, trial staff must store them in a secure place with access limited to authorised people – the trial staff, the sponsor's monitors and auditors, the IRB/IEC, and regulatory authorities. An investigator who undertakes more than one trial at the same time should keep the trials physically apart while they are in progress in the unit. In addition, the monitors and auditors of different sponsors should have separate spaces in which to work during site visits.

## 14.2. Trial subjects

The investigator should give each trial subject a unique identifier to conceal the subject's identity when recording and reporting trial related data. However, the investigator must identify the subject when contacting the subject's personal doctor.

If employees or students of the company or institution that is sponsoring or carrying out the trial wish to take part in it, the investigator should forewarn them of the possible implications of having their personal data processed at work by their colleagues.

## 14.3. Personal Data Protection Act

The Personal Data Protection Act<sup>(17)</sup> covers the processing of personal data, whether written or electronic, of trial subjects. The investigator should comply by:

- Obtaining the subjects' consent for their personal data to be processed
- Using personal data only for the purposes set out in the protocol and the information and consent form
- Making sure that personal data are relevant to the trial, accurate, not excessive and kept for no longer than necessary
- Keeping paper and electronic documents in lockable offices, archives or storage cabinets, and allowing access only to authorised people
- Making sure that personal data stored on computers are secure so that only authorised people can change or delete them
- Telling subjects in the information and consent form that they may see information about themselves on request
- Entering details in a national register, when available

#### **14.4. Malaysian Guidelines on the Use of Human Biological Samples for Research**

Investigators must have informed consent from the trial subjects and approval from the IRB/IEC to take any samples of tissue, blood and body fluids.<sup>(19)</sup>

Consent may be sought for long-term storage and future research as well as for use in the specific trial. Under the Malaysian Guidelines on the use of Human Biological Samples for Research,<sup>(19)</sup> IRB/IEC approval makes it lawful to store and use the samples for the specific trial only. Sponsors who continue to store samples after the trial has ended – both for their own research or to distribute to other researchers – are acting as a tissue bank and must obtain approval from IRB/IEC.

# 15: Compensation, indemnity and insurance

## 15.1. Compensation

Special provisions should apply to providing compensation to volunteers involved in healthy volunteer studies and patient studies.

The nature of the compensation policy should be clear from the information and consent form, and subjects should be invited to seek explanation of any aspect of the undertaking that is not clear to them. Compensation should be related to the time involved and the inconvenience that the volunteer is subjected to. For additional information refer to Section 9.4.

The procedure for reimbursement and compensation should be clearly defined in the volunteer information form.

## 15.2. Indemnity

Before the start of a Phase I trial, the sponsor must indemnify the investigator against any loss incurred by the investigator (including the cost of legal representation) as a result of claims arising from the trial, except to the extent that such claims arise from the negligence of the investigator for which the investigator remains responsible.

## 15.3. Clinical trial insurance

In relation to the sponsor's obligation to comply with the above compensation policy, the sponsor must ensure that a clinical trial insurance is in place to cover its liability and that of the investigator.

The Phase I unit must have insurance to cover claims for negligence, or must provide evidence of financial resources to meet any such claim. Also, physicians involved with the trial must have insurance – such as that offered by a medical defence organisation – that will respond to any negligence claim.

The sponsor and investigator must be able to satisfy the IRB/IEC and NPRA that subjects who take part in a Phase I trial are adequately protected against injury.<sup>(10)</sup> In addition, the sponsor and investigator should do everything possible to ensure that a subject who is involved in a compensation claim is dealt with sympathetically and quickly.



## 16: Safety reporting

The sponsor has overall responsibility for monitoring the safety of its IP. The investigator and sponsor should work together to help the sponsor meet their obligations.

The investigator must:<sup>(10)</sup>

- Record all AEs, including abnormal laboratory results, as instructed in the protocol
- Report to the sponsor, within the time frame identified in the protocol, all serious adverse events (SAE), except those identified as exempt in the protocol or investigator's brochure
- Report to IRB/IEC, within the time frame as per IRB/IEC requirements/SOP all SAEs
- Forward SUSAR reports received from sponsor to IRB/IEC. Provide supplementary or follow up information as and when requested by IRB/IEC
- Provide follow-up reports of SAEs to sponsor and IRB/IEC, and any other information requested, within the time frame identified in the protocol or IRB/IEC requirements or SOP respectively

The sponsor must:

- Report to the NPRA (excluding FIH studies):<sup>(10)</sup>
  - Suspected unexpected serious adverse reactions (SUSARs) that occur in the trial and are associated with any IP used in the trial
  - SUSARs that are associated with any IP used in the trial and that the sponsor learns about from other sources, for example, a SUSAR that occurs in another trial
- Report to the investigator(s):
  - SUSARs, as they occur, without unblinding the investigator

All SAEs in FIH studies must be reported to NPRA and the IRB/IEC.

Where a trial is conducted in more than one site/country or a different trial with the same IP is undertaken elsewhere, the sponsor's reporting duties extend to all other involved investigators, ethics committees, and health authorities.

**Submissions shall be done in accordance to requirements in the Malaysian guidelines for investigational product safety monitoring (excluding FIH studies).<sup>(10)</sup>**

Sponsors may delegate their responsibilities to the investigator, providing the investigator is not unblinded in the process.

# 17: Pathology laboratory

## 17.1. General

All units should have access to a pathology laboratory for assays of blood, urine and other body fluids. Some units may have their own laboratory, whereas others may use a subcontractor. The laboratory should have external accreditation, such as Good Clinical Laboratory Practice (GCLP), College of American Pathologists (CAP), Clinical Pathology Accreditation (CPA) or ISO 17025, or ISO 15189.

It should be inspected regularly and participate in a continual improvement scheme.

## 17.2. Premises, facilities, equipment and procedures

The pathology laboratory should:

- Be purpose-built or adapted for the purpose
- Have automated equipment for routine haematology, biochemistry and serology tests
- Have procedures for analyser calibration and quality control
- Regularly maintain all the equipment, including point-of-care equipment
- Have a procedure for transporting samples safely and quickly from clinical areas to the laboratory
- Have written procedures for all assays, and validate the assays
- Have a stock control procedure to make sure that reagents and consumables are used within their expiry dates
- Keep records, including source documents and final reports
- Have a procedure for authorising and releasing results
- Have a procedure for 'flagging' and notifying medical staff of abnormal results
- Have a laboratory information management system, and validate and backup the system
- Provide protective clothing and safety equipment for staff
- Have a central alarm system for all fridges and freezers
- Have an internal audit programme

## 17.3. Staff

The number and type of laboratory staff will depend on the workload, the complexity of the work, and the extent to which the equipment is automated and computerised.

Laboratories usually have a head of department, with a professional qualification such as Member of the Royal College of Pathologists (MRCPATH) or Master of Pathology (MPATH) or equivalent, who is responsible for the scientific and technical work, staff management and training, and administration.

There should be enough trained and competent staff to ensure a good service for specimen turnaround times, completion of acute work on the day of its receipt, and arrangements for urgent specimens.

All staff must follow the laboratory's standard operating procedures (SOP) and should receive training in quality management systems.

# 18: Data Management, statistics, report and publication

## 18.1. General

The sponsors may do their own data management and statistics on trial data or may subcontract it to a unit with the right facilities and staff. Whoever does it the credibility of the numerical results of the trial depends on the quality and validity of the methods and software used.

## 18.2. Data management

Data management includes data entry, storage, verification, correction and retrieval. Data managers should:

- Have computer systems that are:
  - Validated, secure and allow only authorised access to the data, and
  - Contain an internal audit trail, so that all changes to the data are documented and that entered data are not deleted
- Back up each trial database
- Test the database setup and verification checks for each trial with dummy data before any trial data are entered
- Enter the data twice, or once with 100% check of data
- Keep records of all queries and their resolution
- Have a formal procedure for locking and unlocking the database

Data released to Data Monitoring Committees/Data Safety Monitoring Boards for the purpose of making dose escalation decisions should undergo quality control and be kept in the Trial Master File.

## 18.3. Statistics

There should be a statistical analysis plan (SAP) for each trial. The analysis plan could either be a stand-alone document or be integrated into the protocol. A statistician should:

- Write and sign off on the analysis plans before the trial data is available and before any analysis has started
- Describe in the protocol or SAP the hypotheses being tested and how conclusions will be drawn, the analyses that will be done, the procedures for dealing with missing data and avoiding bias, and the selection of subjects to be included in the analyses.
- Put sample tables and listings in the SAP, to show how data will be presented
- Include any planned interim analyses in the SAP
- Describe and justify in the trial report any deviations from the SAP

- Ensure all steps of the data management, reporting and analysis process have fully validated procedures to avoid the potential for errors. These procedures would normally be included in a company's Standard Operating Procedures library

The Report of the Royal Statistical Society gives guidance about the statistical aspects of FIH trials.<sup>(20)</sup>

#### **18.4. Report and publication policy**

Whether the trial is completed or stopped prematurely, the sponsor should ensure that an end-of-trial report is prepared from the data and is given to the investigator, for comments and signature. The report should be based on the ICH Guideline (E9) for Clinical Study Reports and has to be submitted to the NPRA within one year of the end of the trial.

The trial findings should be published, as an electronic and/or paper document, within a reasonable time after the end of the trial. The sponsor and investigator should agree the publication policy in the protocol or contract, before the start of the trial.

The sponsor must be allowed enough time to obtain any patent protection. Either party may prepare a manuscript for publication in a peer-reviewed journal as per agreement. Authorship should reflect work done by both parties, in accordance with recognised principles of scientific collaboration.

#### **18.5. Staff**

Suitably qualified and experienced statistician, data managers and data entry staff should be recruited.

Data managers should be life science graduates or of similar status.

An expert in PK should interpret the PK data.

# 19: Essential documents, trial master file and archiving

## 19.1. Trial master file

The investigator must keep a trial master file of essential documents that:

- Allow the monitor, auditor, IRB/IEC or regulatory authority to directly access all requested trial-related records to ensure compliance with applicable regulatory requirements.<sup>(11)</sup>

Essential documents should be:

- Generated and be on file before the trial starts
- Added to the files during the trial, to show that any new information is documented as it becomes available
- In the file after the end of the trial

## 19.2. Quality of documents

Essential and supporting documents:

- Should be accurate, complete, legible and timely with the data reported to the sponsor in the case report forms (CRF) and all required reports, and readily available upon request<sup>(11)</sup>
- Should not be altered without permission and creation of an audit trail, particularly if the documents are stored on electronic, magnetic, optical or similar media
- May be copied or transferred to other media for archiving, if the method has been validated to ensure that information will not be lost or altered and if the copies or transfers are certified for accuracy and completeness
- Should be readily available in printed form, if stored on media that require processing

## 19.3. Storage of documents

A specific person, designated as an archivist, should store trial documents. The archivist should:

- Have enough dedicated space that is suitable to store documents from all current trials on site and to store documents from all completed trials either on-site or off-site in a commercial archive
- Have storage facilities that are secure and adequately protected from fire, flood, pests, extremes of temperature and humidity, and unauthorised access
- Inform the sponsor about the arrangements for storing documents, and about any changes to the arrangements
- Notify the sponsor if the investigator becomes unable to store trial documents, so that the sponsor can arrange for them to be stored elsewhere

#### **19.4. Duration of storage**

Essential and supporting documents, including the trial subjects' records, must be archived for the period specified by regulatory requirements and GCP guidelines. Access to documents must be restricted to the people with responsibility for archiving.

#### **19.5. Disposal of documents**

- Any document pertaining to the trial must not be destroyed without the prior permission of the sponsor
- When any document is destroyed, the reasons for the disposal should be documented appropriately
- The sponsor should inform the Phase I unit about the completion of the retention period of the documents

## 20: Project management and monitoring

Sponsors should allocate a project manager to every Phase I trial to manage the administrative aspects and general coordination of the trial. In addition, a study monitor is allocated to verify that the study activities are compliant with the protocol and GCP. Some sponsors may have one person do both jobs.

### 20.1. Qualifications of the project manager and monitor

The project manager and monitor should have GCP training which is approved by the National Committee for Clinical Research (NCCR) that incorporates the stipulated curriculum<sup>(11)</sup>, the relevant aspects of GMP and monitoring, as appropriate.

In a Phase I trial, a lot of data are collected from few subjects. Unforeseen findings often need protocol amendments to keep a trial running. Additionally, a unit may have to manufacture, assemble or import the IP. Hence, the tasks of project manager and/or monitor should include:

- Knowing the pre-clinical data and being able to deal with any concerns that the investigators might have about the risk assessment, by arranging for them to discuss their concerns with the sponsor's physician or pre-clinical staff
- Assisting the investigator in obtaining from the sponsor in good time any documents required to support applications to the IRB/IEC or NPRA<sup>(10)</sup>
- Ensuring that all the trial documents and the IP are delivered in good time for the trial to start on schedule
- Monitoring the trial for GMP compliance – if the unit manufactures, assembles or imports the IP – as well as for GCP compliance
- Scheduling the monitoring visits for key days of the trial, such as when the IP is first administered, the dose is increased or a non-IP is administered
- Getting the sponsor to provide the investigator in good time with any pharmacokinetic data that are needed before the dose can be increased in a dose-rising trial
- Participating in and documenting, if appropriate, any discussions between the sponsor and the investigator before the dose is increased, and ensuring that the protocol is followed



## 21: Quality management

### 21.1. Quality system

Although, the ultimate responsibility for the quality and the integrity of the trial data lies with the sponsor, all units involved should have their own GCP compliant system for quality control and quality assurance, such as ISO standards.

All units should have written and authorised procedures.

- At each point of use, a current version of each procedure should be kept
- Obsolete versions should be removed from circulation. However, a copy must be available for reference
- Procedures must be reviewed regularly
- New procedures or any change in procedures should be informed to the relevant staff, who should be trained as necessary.
- Records must be kept and be traceable to the version of a procedure that was current at any given time.

### 21.2. Quality control

Each stage of the trial must be checked for quality by the relevant staff to ensure that the regulations are followed and that accurate data are generated.

### 21.3. Auditors

Auditors should:

- Be trained in auditing
- Be independent of whatever they audit – if a unit does not have its own independent auditor, the sponsor or a subcontractor may conduct the audit
- Regularly audit the quality system
- Audit the validation of computerised systems
- Regularly audit the facilities, and frequently-used subcontractors such as laboratories, against the relevant guidelines
- Know the details of the unit's quality system and the guidance documents of GCP, GMP, NPRA regulations<sup>(10)</sup>, and other relevant documents
- Check whatever tasks have been delegated to the investigator by the sponsor against those documents as well as the protocol
- Devise and follow an audit plan based on the type and complexity of the trial, the number of subjects and any problems encountered

#### **21.4. Audits**

A full clinical trial audit should include:

- The CTIL/CTX and IRB/IEC applications<sup>(10)</sup>
- The trial documents – protocol, information and consent form, blank CRF, and the trial report
- The trial procedures
- The presence, completeness and accuracy of essential documents in the trial master file
- The CRFs and source documents
- The trial database and statistical analysis
- A written report of the audit findings for the investigator and other relevant staff, and
- An audit certificate for the trial master file

The sites must follow-up with appropriate corrective and preventive actions (CAPA) and provide a report of the actions to the auditors.

#### **21.5. Sponsor's auditors**

The sponsor must carry out regular auditing of the unit's facilities or systems, or a specific trial as and when necessary.

# Appendix 1. Preclinical Information to be considered for FIH clinical trials<sup>(6)</sup>

## 1. Demonstration of relevance of the animal model

Qualitative and quantitative differences may exist in biological responses in animals compared to humans.

Where there is evidence of species-specificity of action from *in vitro* studies with human cells compared with cells from a test species, the value of the *in vivo* response of the test species may be significantly reduced in terms of predicting the *in vivo* human response. It should be noted that a similar response in human and animal cells *in vitro* is not necessarily a guarantee that the *in vivo* response will be similar.

In practice this means that animal studies with highly species-specific medicinal products may:

- Not reproduce the intended pharmacological effect in humans
- Give rise to misinterpretation of PK and PD results
- Not identify relevant toxic effects

## 2. Pharmacodynamics

PD studies should address the mode of action, and provide knowledge on the biology of the target. These data will help to characterise the pharmacological effects and to identify the most relevant animal models. The primary and secondary PD, should be conducted in *in vitro* animal and human systems and *in vivo* in the animal models. These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, duration of effect and dose-response.

A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps in order to increase the likelihood to detect significant pharmacological effects with low doses and to identify active substances with U-shaped or bell-shaped dose-response curves. Such significant or even reverse effects have been reported with biological compounds.

## 3. Pharmacokinetics

Standard PK and toxicokinetic data should be available in all species used for safety studies before going into humans. Exposures at pharmacological doses in the relevant animal models should be determined especially when PD effects are suspected to contribute to potential safety concerns.

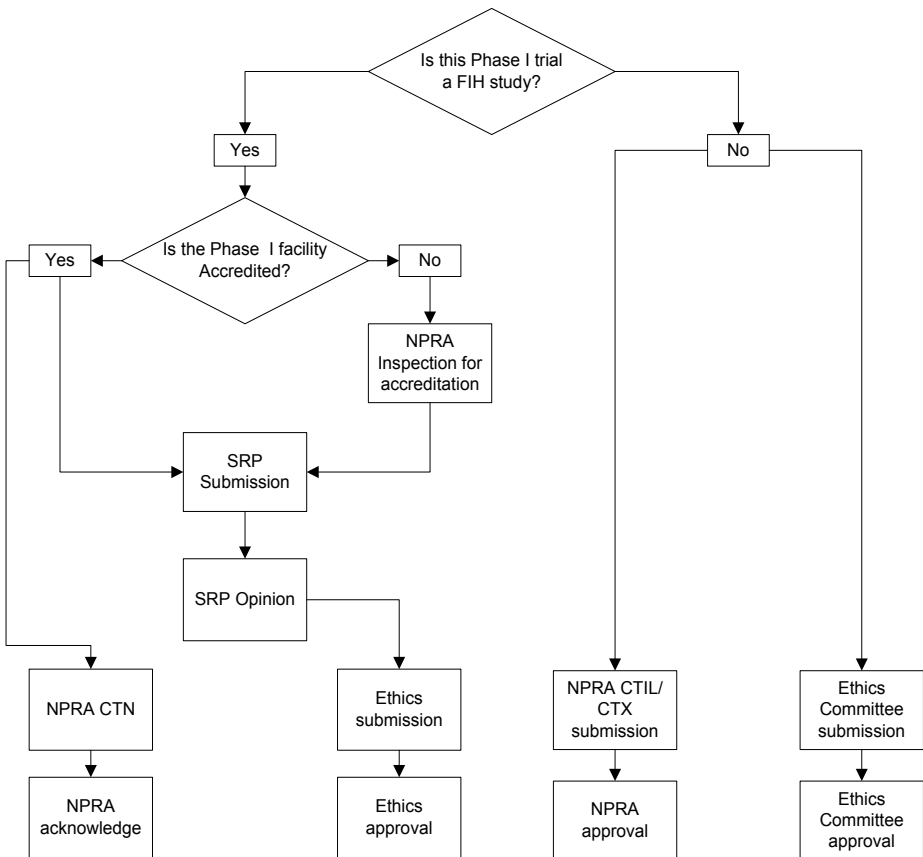
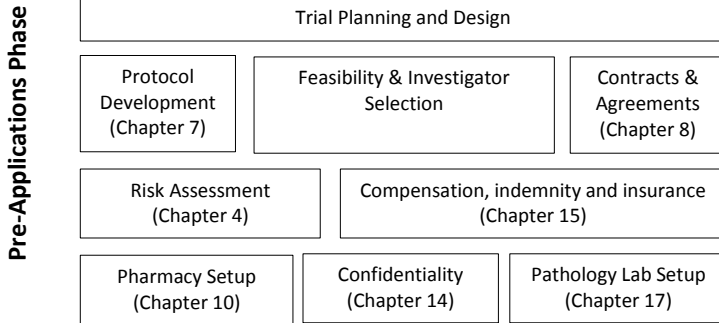
## 4. Safety Pharmacology

Standard core battery data should be available before the first administration in humans. Additional studies to investigate effects in other organ systems should be carried out on a case-by-case basis. In particular, for medicinal products targeting the immune system, potential unintended effects should be investigated, e.g. using *in vitro* studies, including human material.

## 5. Toxicology

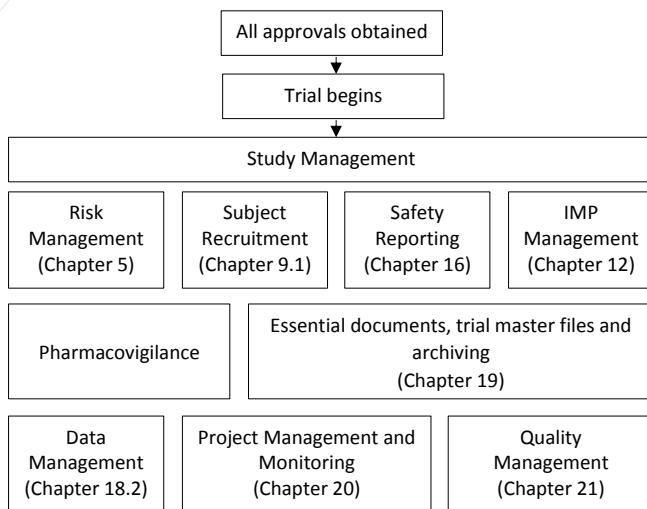
The toxicology programme should be performed in relevant animal species and include toxicokinetics. When factors influencing risk are identified, the inclusion of additional endpoints should be considered, on a case-by-case basis. Toxicity studies in non-relevant species may give rise to misinterpretation and are discouraged. The use of homologous products or a transgenic model approach or of *in vitro* human cell systems could provide relevant additional information. It should be noted that human specific proteins are likely to be immunogenic in animal species. Therefore, repeat dosing studies in animals may not predict the effects of such substances in humans (e.g. presence of neutralising antibodies).

## Appendix 2: Process for initiating Phase I (including FIH and First Dose in Human) clinical trials in Malaysia



FIH: First-in-human; CTN: Clinical Trial Notification; CTIL/CTX: Clinical Trial Import License/Clinical Trial Exemption (for manufacturing); SRP: Scientific Review Panel; NPRA: National Pharmaceutical Regulatory Agency.

**Post-Applications Phase**



## Appendix 3: Scientific and medical literature

- The scientific and medical literature is a significant source of information to monitor the safety profile and of the risk-benefit balance of medicinal products. This is particularly important in the detection of new safety signals or emerging safety issues.
- **Product registration holders**
  - Are expected to be aware of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week.
  - Should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties.
  - Should also have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate.
- Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by project registration holders to identify and record individual case safety reports originating from spontaneous reports or non-interventional post-authorisation studies. If multiple medicinal products are mentioned in the publication, only those, which are identified by the publication's author(s) as having at least, a possible causal relationship with the suspected adverse reaction should be considered by the concerned project registration holder(s).

## Appendix 4: List of custodians

Body	Name	Website Link
Regulatory body	National Pharmaceutical Regulatory Agency (NPRA)	<a href="http://nptra.moh.gov.my">http://nptra.moh.gov.my</a>
	Medical Device Authority (MDA)	<a href="http://www.mdb.gov.my/mdb/">http://www.mdb.gov.my/mdb/</a>
	Division of Disease Control Ministry of Health	Application process through BLESS: <a href="https://open.bless.gov.my/bless/">https://open.bless.gov.my/bless/</a>
Central and Institutional Review Board (IRB)/ Independent Ethics Committees (IEC)	Medical Research Ethics Committee (MREC)	<a href="http://nih.gov.my/web/mrec/">http://nih.gov.my/web/mrec/</a>  Application process through NMRR: <a href="https://www.nmrr.gov.my/fwLoginPage.jsp">https://www.nmrr.gov.my/fwLoginPage.jsp</a>
	Joint Penang Independent Ethics Committee (JPEC)	<a href="http://info-kinetics.com/jpec">http://info-kinetics.com/jpec</a>
	Medical Ethics Committee, University Malaya Medical Centre (MEC,UMMC)	<a href="https://eservices.ummc.edu.my/ire-search/login.asp">https://eservices.ummc.edu.my/ire-search/login.asp</a>
	Independent Ethics Committee Sime Darby Healthcare (IECSDH)	<a href="http://www.ramsaysimedarby.asia/eng/about-us/independent-ethics-committee">http://www.ramsaysimedarby.asia/eng/about-us/independent-ethics-committee</a>
	Sunway Medical Centre Independent Research Ethics Committee (SREC)	<a href="http://sunwaymedical.com/about-clinical-research-centre/12255-2/">http://sunwaymedical.com/about-clinical-research-centre/12255-2/</a>
	International Medical University (IMU) Joint Committee of the Research and Ethics Committee (IMUJC)	<a href="http://irdi.imu.edu.my/policies-and-guidelines">http://irdi.imu.edu.my/policies-and-guidelines</a>
	Jawatankuasa Etika Penyelidikan Institut Jantung Negara (IJN)	<a href="http://www.ijn.com.my/education/clinical-research/">http://www.ijn.com.my/education/clinical-research/</a>
	IIUM Research Ethics Committee (IREC)	<a href="http://iiumedic.net/irec/v1/">http://iiumedic.net/irec/v1/</a>
	Jawatankuasa Etika Penyelidikan, Universiti Teknologi MARA (UiTM)	<a href="http://ethicsrmi.uitm.edu.my/ethicsrmi/index.php?option=com_contact&amp;view=contact&amp;id=1&amp;Itemid=66">http://ethicsrmi.uitm.edu.my/ethicsrmi/index.php?option=com_contact&amp;view=contact&amp;id=1&amp;Itemid=66</a>
	Jawatankuasa Etika Universiti Untuk Penyelidikan Melibatkan Manusia, Universiti Putra Malaysia (JKEUPM)	<a href="http://www.rmc.upm.edu.my/jkeupmbm">http://www.rmc.upm.edu.my/jkeupmbm</a>
	Jawatankuasa Etika Penyelidikan (Manusia), USM [JEPeM]	<a href="http://www.jepem.kk.usm.my/">http://www.jepem.kk.usm.my/</a>
	Jawatankuasa Etika Penyelidikan, Universiti Kebangsaan Malaysia (JEPUKM)	<a href="http://www.ppek.ukm.my/sppi/maut-turun-borang-penyelidikan/">http://www.ppek.ukm.my/sppi/maut-turun-borang-penyelidikan/</a>
	Government support bodies	National Committee for Clinical Research (NCCR)
Clinical Research Centre (CRC)		<a href="http://www.crc.gov.my/">http://www.crc.gov.my/</a>
Clinical Research Malaysia (CRM)		<a href="http://www.clinicalresearch.my/">http://www.clinicalresearch.my/</a>



## Glossary

The list below comprises some important terms with its explanation taken from the Malaysian Guideline for Good Clinical Practice document.

Clinical Trial Exemption (CTX)	An approval by the DCA authorising the applicant to manufacture any local product for the purpose of clinical trial. <sup>(11)</sup>
Clinical Trial Import License (CTIL)	A license in Form 4 in the schedule of The Control of Drugs and Cosmetics Regulations of 1984, authorising the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product. <sup>(11)</sup>
Good Manufacturing Practice (GMP)	A standard that should be followed by manufacturers of registered pharmaceutical/ traditional products and notified cosmetics to ensure that the product manufactured is safe, efficacious and of quality. <sup>(10)</sup>
Investigational product (IP)	A pharmaceutical form of an active ingredient including herbal/ animal medicinal products or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use. <sup>(11)</sup>
Suspected Unexpected Serious Adverse Reaction (SUSAR)	<p>The acronym SUSAR typically means “suspected, unexpected, serious adverse reaction,” although the exact order of the words may vary, such as “serious unexpected suspected adverse reaction” and “suspected serious unexpected adverse reaction.” The term is often used to identify serious adverse reactions that require reporting to a regulatory authority. The specific requirements for reporting would depend on the regulatory agency(ies) involved.<sup>(21)</sup></p> <p>The criteria for reporting SUSARs to the DCA in the Malaysian context are as follows:<sup>(10)</sup></p> <ul style="list-style-type: none"> <li>(a) The event is an adverse drug reaction (ADR).</li> <li>(b) The suspected drug is the investigational product, which requires CTIL/CTX, not the comparator or placebo.</li> <li>(c) The ADR is serious.</li> <li>(d) The ADR is unexpected.</li> <li>(e) The source of report can be either local or overseas. In case of overseas report, it must come from the same clinical trial protocol as in Malaysia.</li> <li>(f) The report must contain the minimum information for expedited reporting.</li> </ul>

## References

1. Association of British Pharmaceutical Industry. Guidelines for phase I clinical trials. 2012.
2. Thorat S, Banarjee S, Gaikwad D, Jadhav S, Thorat R. Clinical trial: review. *International Journal of Pharmaceutical Sciences Review and Research*. 2010.;1(2):101-6.
3. Independent Institute, FDAReview.org. The drug development and approval process. Available at: [http://www.fda-review.org/03\\_drug\\_development.php](http://www.fda-review.org/03_drug_development.php). Accessed on: 01 December 2016.
4. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research. Guidance for industry, investigators and reviewers: exploratory IND studies. 2006.
5. National Key Economic Areas. Healthcare NKEA fact sheet. Available at: [http://etp.pemandu.gov.my/upload/NKEA\\_Factsheet\\_Healthcare.pdf](http://etp.pemandu.gov.my/upload/NKEA_Factsheet_Healthcare.pdf). Accessed on 07 October 2016.
6. European Medicines Agency. Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products. 2007.
7. European Medicines Agency. ICH Topic S 3 A. Note for guidance on toxicokinetics: a guidance for assessing systemic exposure in toxicology studies (CPMP/ICH/384/95). 1995.
8. Prentis R, Lis Y, Walker S. Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964-1985). *Br J Clin Pharmacol*. 1988;25:387-96.
9. Shah R. The significance of QT interval in drug development. *Br J Clin Pharmacol*. 2002.;54:188-202.
10. Malaysian Guideline for Application of CTIL and CTX. Available at: [http://npra.moh.gov.my/images/Guidelines\\_Central/Guidelines\\_on\\_Clinical\\_Trial/2016/CTIL\\_CTX\\_Guideline\\_Edn\\_6.3\\_clean.pdf](http://npra.moh.gov.my/images/Guidelines_Central/Guidelines_on_Clinical_Trial/2016/CTIL_CTX_Guideline_Edn_6.3_clean.pdf). Accessed on: 28 August 2016.
11. Ministry of Health Malaysia. Malaysian guideline for good clinical practice. 3rd ed. 2011.
12. U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult health volunteers. 2005.
13. European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. 2016.
14. Medicines & Healthcare products Regulatory Agency. Phase I accreditation scheme requirements. 2015.
15. Sibille M, Donazzolo Y, Lecoz F, Krupka E. Letter too the editors: After the London tragedy, is it still possible to consider Phase I is safe? *Br J Clin Pharmacol*. 2006.;62(4):502-3.
16. Butler D, Callaway E. Scientists in the dark after fatal French clinical trial. *Nature*. 2016.:263-4.
17. Laws of Malaysia. Act 709. Personal Data Protection Act. 2010.
18. Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme. Guide to good manufacturing practice for medicinal products, part II. 2015.
19. Ministry of Health Malaysia. Malaysian guidelines on the use of human biological samples for research. 2015.
20. Royal Statistical Society. Report of the Working Party on Statistical Issues in first-in-man studies. 2007.
21. United States Food and Drug Administration, FIRST Clinical Research. International SUSAR. Available at: [https://firstclinical.com/fda-gcp/?show=2012/International\\_SUSAR&format=fulllist](https://firstclinical.com/fda-gcp/?show=2012/International_SUSAR&format=fulllist). Accessed on 25 May 2017.

## Acknowledgment

The writing committee would like to express their thanks to the following for their contribution during the development of these guidelines:

- Dr. Linda Hakes and Prof Chim Lang, for their valuable contribution as Subject Matter Experts.
- Clinical Research Malaysia for organising and facilitating the committee meetings.
- The clinical trial units/medical departments/regulatory departments of the pharmaceutical industry for their feedback.
- All those who have contributed either directly or indirectly to the development of this document.

## Disclosure statement

The members of this writing committee do not have potential conflicts of interest. Dr. Linda Hakes holds shares in Eli Lilly and Company; and UCB S.A.



[www.clinicalresearch.my](http://www.clinicalresearch.my)



Published by,

**CLINICAL RESEARCH MALAYSIA**

Suite E-10-20, Amcorp Business Suites,  
Menara Melawangi, Amcorp Trade Centre,  
No. 18, Jalan Persiaran Barat,  
46050 Petaling Jaya,  
Selangor Darul Ehsan, Malaysia.

Tel: +60379605153  
Fax: +60379321940