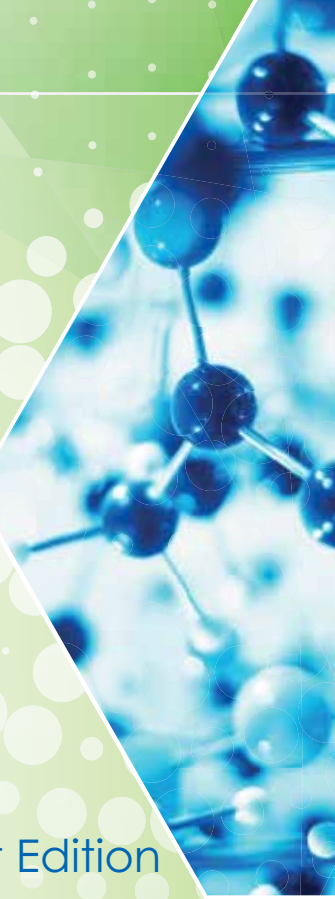
Persatuan Penyelidik Klinikal Profesional Malaysia

SCRPM

Society of Clinical Research Professionals Malaysia

A GUIDE TO CONDUCTING CLINICAL TRIALS IN MALAYSIA



2016 First Edition

Foreword by Minister of Health Malaysia

The total drug discovery and development market size in the top seven Asian countries was estimated at $5.3 billion in 2011 and is forecast to reach $17.3 billion by the end of 2018. Globalization in the clinical trial industry has led to an increased number of trials being conducted in emerging markets. In Malaysia, the growth of Industry Sponsored Research (ISR) have enjoyed a steady and considerable increase in number from around 143 trials in 2010 to 201 trials in 2015, a 41% rise in just 5 years.

Malaysia is viewed as a country of choice for conducting clinical trials in terms of having a well-developed and modern healthcare infrastructure, a growing pool of qualified and well-trained investigators and support staff, robust ethical reviews by the ethics committee, regulatory oversight by the National Pharmaceutical Control Bureau (NPCB) and competitive trial cost per patient compared to neighboring countries. As the icing on the cake, Malaysia's multi-ethnic population provides sponsors and Contract Research Organizations (CROs) with access to genetic diversity while there is strong support and commitment from the Malaysian Government.

To remain competitive with its neighboring peers, Malaysia has taken multipronged approaches to attract higher quality trials to its shores. These include building the capability and capacity of Ministry of Health (MOH) sites to conduct clinical trials, formation of a National Committee for Clinical Research (NCCR) to regulate clinical research, the corporatization of Clinical Research Malaysia (CRM) to function as an enabler and facilitator to the clinical research industry, strengthening of the regulatory framework to support ethical research and increasing the regulatory oversight on clinical trials.

Indeed, this Guide to Conducting Clinical Trials in Malaysia is a remarkably thorough and notably clear compilation of updated information and guidance on conducting clinical trials in Malaysia. As we embark upon an era of high expectation in the provision of much-needed innovative medicines, this guidebook is to be commended for its timely production of professional guidance that will underpin a smooth and effective conduct of clinical trials in Malaysia.

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

A Note from the President of the Society of Clinical Research Professionals Malaysia (SCRPM)

On behalf of the society I am pleased to be able to provide this guidebook to you. This guidebook is the result of much research and effort of the society members, who are not only knowledgeable in the regulatory aspects and logistics in conducting clinical trials in Malaysia, but have also experienced and conducted a number of successful GCP compliant clinical trials here by themselves.

We cover all aspects of Industry Sponsored Research, starting with an overview of the Clinical Research Environment, highlights of the main differences between the Malaysian GCP Guidelines and the ICH-GCP Guidelines, the regulatory requirements, the various ethical committees and requirements, Clinical Trial Agreement and budget, custom requirements on importing and exporting clinical trial specimens, supplies and medical devices, insurance and indemnity.

This is the first edition and we hope to continuously update it by providing the link to the various institutions' website, so that the latest information is always available. We hope that you will find this helpful and would value your feedback for us to improve on the future editions.

Lastly, I would like to thank all who have contributed to this guidebook and the reviewers from the various institutions who validated the accuracy of the contents and Clinical Research Malaysia (CRM) for sponsoring the printing of the books.

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1 Overview of Clinical Trials in Malaysia

Background and Overview

Malaysia occupies a unique position in South East Asia with a population size of approximately 31.2 million (estimated) as of January 2016. The ethnic composition of Malaysia is diverse and composed of ethnic Malays (50%), Chinese (23%), Indians (8%) and the indigenous population (12%)[1].

The number of live births recorded in 2014 was 511,865, with an increase of 1.6 per cent compared to 2013 (503,914). The crude birth rate remained unchanged at 16.7 per 1,000 population for both years. The total fertility rate was 2.0 births per woman aged 15–49 years for the same period. Life expectancy at birth of Malaysian residents continues to rise every year. In 2015, a newborn is expected to live to 74.8 years, increased by 0.7 years compared to 74.1 years in 2010[2].

Overall, the annual population Growth Rate remains consistent at about 1.5%[3].

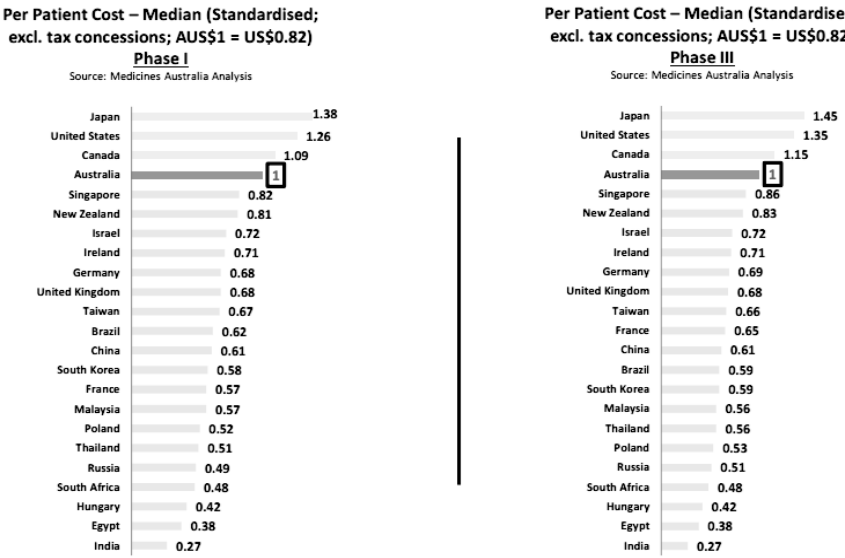
These demographic factors combined with high literacy rates of 93.1% amongst Malaysians and proficiency with the use of English as the key medium of instruction amongst medical practitioners should in theory make Malaysia an attractive venue for clinical research. Additionally, the cost of conducting clinical trials in Malaysia remains relatively competitive within the region (Fig 1).

[1]Department of Statistics Malaysia

[2]Department of Statistics Malaysia

[3]Data from worldbank.org

Fig 1[4]:



Clinical trial conduct in Malaysia has continued to grow albeit at a slower rate compared to other countries in the region (Fig 2). Reasons for this are multifactorial but generally include sponsor company interests in countries with high population growth or economic potential like China or countries with excellent medical infrastructure, which allows for high-quality research to be conducted (example Korea and Singapore).

[4]Source : Dr Martin Cross, Medicines Australia

Fig 2:

The Total Health Expenditure (THE) for Malaysia during 1997-2013 ranged from RM8,303 million in 1997 to RM44,748 million in 2013. The health spending as a share of Gross Domestic Product (GDP) for the same period ranged from 2.95 per cent to 4.53 per cent of GDP. Health spending in the public sector was higher than the private sector throughout the years. Overall, the per capita spending on health ranged from RM630 (USD224) in 1997 to RM1,494 (USD474) in 2013. The total General Government Health Expenditure (GGHE) as percentage of General Government Expenditure (GGE), increased from RM4,430 million in 1997 to RM23,254 million in 2013 or an increase from 4.91 per cent to 6.29 per cent over the time period. Despite the increase, healthcare spending as a share of GDP is still relatively low compared to developed countries[5].

[5]Malaysia National Health Accounts Health Expenditure Report 1997-2013

The impetus as such was for the government of Malaysia to grow research and create a conducive ecosystem to support a healthy and robust clinical research industry in Malaysia.

Launched on 25 September, 2010, the Economic Transformation Programme (ETP) was formulated as part of Malaysia's National Transformation Programme. Its goal is to elevate the country to developed-nation status by 2020, targeting Gross National Income (GNI) per capita of US$15,000. This will be achieved by attracting US$444 billion in investments which will, in turn, create 3.3 million new jobs[6].

Industry Sponsored Research was mooted as part of the ETP initiative under Entry Point Project (EPP) 2: Creating a Supportive Ecosystem to Grow Clinical Research. The aim of this project is to achieve GNI of RM578.4 million and the creation of 905 new jobs by 2020. While acknowledging that Malaysia is indeed lagging behind its peers, steps are being implemented to change this, and a target has been set to achieve at least 1,000 clinical trials by 2020. This EPP therefore focuses on developing a supportive clinical research ecosystem that allows for more efficient and higher quality trials.

The following are some of the government initiatives taken to promote and develop industry sponsored research:

- Development of Malaysian Good Clinical Practice Guidelines in 1999 and mandating Good Clinical Practice (GCP) certification for all investigators participating in clinical research. The guidelines have been updated twice in 2004 and 2011, respectively.

- The formation of a National Committee for Clinical Research (NCCR) in 1997 focusing on Policy Shaping. The committee meets at least twice annually and is chaired by the Director General of Ministry of Health (MOH). The NCCR , Ministry of Health, is spearheading various initiatives to enhance and regulate the quality of biomedical research and clinical research practice in Malaysia. The NCCR is made up of member representatives and experts from the Ministry of Health (MOH), various national Universities, the Malaysian Pharmaceutical Society (MPS), the Pharmaceutical Association of Malaysia (PhAMA), the Malaysian Organisation of Pharmaceutical Industries (MOPI), as well as other Non-Governmental Organisations.

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[6]etp.pemandu.gov.my

This composition of member representatives reflects the ongoing "smart-partnerships" amongst the various stakeholders with interests in quality clinical research in Malaysia. The secretariat for this committee is the Centre for Investigational New Product, based at the National Pharmaceutical Control Bureau. As of June 2008, the hosting duties became the responsibility of the Clinical Research Centre, Ministry of Health[7].

The following list gives examples of some significant contributions from the NCCR:

- Established the guidelines for accreditation of clinical research centres.
- Developed and published the Malaysian Good Clinical Practice (GCP) Guidelines.
- Developed the curriculum and requirement for conducting GCP training courses.
- Initiated and carried out a series of national GCP training courses for trainer/clinical researcher.
- Established the procedure for the accreditation of clinical facilities to conduct GCP compliant studies.
- Undertook preliminary inspection visits to major hospitals/clinical facilities and advised on steps that needed to be carried out to attain compliance.
- Initiated and carried out introductory courses in Good Laboratory Practice
- Developed the guidelines for the conduct of Bio-equivalence evaluation for the generic pharmaceuticals.
- Undertook a review of current practices for ethical approval in Malaysia and established mechanisms to harmonise approval standards and procedure.
- Developed a series of guidelines for the conduct of clinical studies for herbal product.

- Formation of Clinical Research Malaysia (CRM) on 15 June 2012, a dedicated not for profit entity to grow the ecosystem to support industry sponsored research. Clinical Research Malaysia assists research organisations, sponsors and investigators by:
  - Providing a one-stop centre for the conduct of feasibility assessments (and access to the public hospital network of investigators).
  - Assisting in an advisory capacity and acting as a resource centre for interested stakeholders.

[7]http://www.nccr.gov.my/

- Providing financial management support to sponsors and investigators.
- Supporting the infrastructure for research facilities at public hospital and growing the investigator / research personnel base.

- Strengthening the regulatory framework to support ethical research and increase regulatory oversight. The Centre for Investigational New Product (CINP), National Pharmaceutical Control Bureau, has issued clear guidelines for the conduct of research and inspection guidelines in consultation with industry stakeholders to support this end. The agency oversees clinical trials in Malaysia through the granting of Clinical Trial Import Licence (CTIL)/ Clinical Trial Exemption (CTX) and through the conduct of regulatory inspections of sites, sponsors, Contract Research Organization (CRO) and Institutional Review Boards (IRB) in Malaysia. The agency has also developed Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption, Guidelines for Good Clinical Practice Inspection, the Malaysian Guideline for Bioequivalence (BE) Inspection and the Malaysian Guideline for Safety Reporting of Investigational Products.

- Adding research as an area of prioritisation under the 3rd Industrial Masterplan for Malaysia (2006-2020).

Generally, research is conducted in Malaysia at teaching institutions/ university hospitals such as University Malaya Medical Centre, Universiti Kebangsaan Malaysia Medical Centre, Hospital Universiti Sains Malaysia; government hospitals (MOH) institutions; the National Heart Institute and increasingly at private medical centres across the country. The wide network of local MOH health clinics represents a unique opportunity for access to a previously untapped, primary care patient pool.

The Regulatory body that oversees clinical research is the Centre for Investigational New Product, National Pharmaceutical Control Bureau. Regulatory submissions are made in parallel with IRB submissions. The agency has an informative website that is user friendly with easy navigation for quick access to information and resource material.

The IRB structure in Malaysia depends on the location or type of facility conducting the research. Generally speaking, most teaching institutions have their own local IRB/Independent Ethics Committee (IEC), while research conducted at Ministry of

Health hospitals fall under the purview of the central IRB, Medical Research and Ethics Committee (MREC). In 2012, a circular was issued by the Drug Control Authority (DCA) that required all IRB in Malaysia that approve drug related trial to be registered with the DCA. The list of registered IRB's can be found on the National Pharmaceutical Control Bureau (NPCB) website.

2 Differences between International Council on Harmonisation - Good Clinical Practice (ICH-GCP E6 R1) & Malaysian GCP guidelines (Third Edition, 2011)

Malaysian GCP is derived from the core principles of ICH-GCP though there are some differences as cited in the table below to accommodate local regulations/ requirements and cultural practices.

Section	Malaysian GCP	ICH-GCP
Definitions : Section 1 Malaysian GCP includes several additional definitions that are not cited in ICH-GCP Section 1, definition differs slightly from ICH-GCP	1.6 Approved Training in Good Clinical Practice Training which is approved by the National Committee for Clinical Research (NCCR). The content of the training must incorporate the curriculum as stipulated by the committee	Does not have a corresponding definition
	1.13 Clinical Trial Exemption (CTX) An approval by the DCA authorising the applicant to manufacture any local product for the purpose of clinical trial.	Does not have a corresponding definition
	1.14 Clinical Trial Import Licence (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	Does not have a corresponding definition

Section	Malaysian GCP	ICH-GCP
	product is not a registered product.	
	1.26 Drug Control Authority A regulatory authority established for the purpose of regulating the Control of Drugs and Cosmetics Regulations, 1984	Does not have a corresponding definition
	1.29 Herbal /Animal Medicinal Products Plant/animal-derived materials or products with therapeutic or other human health benefits which contain either raw or processed ingredients from one or more plants/ animals	Does not have a corresponding definition
	1.38 Investigational Product A pharmaceutical form of an active ingredient including plant/ animal-derived 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),	ICH-GCP does not include plant/animal-derived medicinal products as part of the definition. **1.33 Investigational Product** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled

Section	Malaysian GCP	ICH-GCP
	or when used to gain further information about an approved use.	unapproved indication, or when used to gain further information about an approved use.
	1.46 National Committee for Clinical Research (NCCR) A committee established for the purpose of coordinating and promoting clinical research in Malaysia, chaired by the Director General of Health, Ministry of Health Malaysia.	Does not have a corresponding definition
Section 3 : Institutional Review Board/ Independent Ethics Committee Section 3.2 Composition, Functions and Operations	An addition Section 3.2.7 allows the Central IRB for the Ministry of Health Malaysia to provide a review for research for any institution that does not have its own IRB	No corresponding clause
	3.2.7. An institution without IRB/IEC may request IRB/IEC of Ministry of Health, Malaysia or the Universities to make decisions on behalf of the said institution	No corresponding clause
Section 4 : Investigator Section 4.1 Investigator Qualifications	Malaysian GCP stipulates that the investigator(s) training in GCP has to be **approved training** as per definition Section 1.6	Does not stipulate specific requirements for approved GCP training

Section	Malaysian GCP	ICH-GCP
	4.1.1 The investigator(s) should be qualified by education, approved training in Good Clinical Practice, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/ IEC, and/or the regulatory authority(ies).	
Section 4.8 Informed Consent by illiterate subjects	Section 4.8.9 pertaining to illiterate subjects/ or legally acceptable representative permits the use of thumbprint 4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written	ICH-GCP has no reference as to the use of a thumbprint for illiterate subjects or legally acceptable representative 4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed

Section	Malaysian GCP	ICH-GCP
	information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and/or thumb printed and dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and appropriately understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.	consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
Section 4.8.10 Elements of the Informed	For cultural considerations Malaysian GCP	No corresponding clause

Section	Malaysian GCP	ICH-GCP
Consent Form	requires the disclosure of the source of the investigational product that may be culturally unacceptable 4.8.10 (u) The source(s) and component(s) of the investigational product(s) that may be culturally unacceptable.	
Section 5: Sponsor Section 5.6.1 Investigator Selection	The sponsor is responsible for selecting the investigator(s)/ institution(s). Each investigator should be qualified by training (including approved GCP training) and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibilities.	The sponsor is responsible for selecting the investigator(s)/ institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibilities.
Section 5.14 Supply and handling of Investigational Product(s)	Malaysian GCP cites the regulatory requirements for importation of the IP	5.14.2 The sponsor should not supply an investigator/institution

Section	Malaysian GCP	ICH-GCP
	stipulating the requirement for the Clinical Trial Import License and customs clearance process. 5.14.2 The sponsor should not supply an investigator/ institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies). All importation of clinical trial drugs should go through customs even though a clinical trial import licence has been obtained.	with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/ favourable opinion from IRB/IEC and regulatory authority (ies)).
Section 5.20 Non Compliance	Malaysian GCP includes a clause concerning the enforcement powers of the Drug Control Authority (DCA) 5.20.3 The DCA will enforce the rules and punitive action will be decided by the DCA.	No corresponding clause

3 Drug Control Authority

The National Pharmaceutical Control Bureau (NPCB) acts as a secretariat to the Drug Control Authority (DCA), Ministry of Health Malaysia (MOH).

NPCB has been designated as a World Health Organization (WHO) Collaborating Centre for regulatory Control of Pharmaceuticals and it is also a participating authority in the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Effective from 29th March 2013, Malaysia is officially a non-member with full adherent to the Organisation for Economic Cooperation and Development (OECD) Council Acts related to Mutual Acceptance of Data (MAD) in the Assessment of Chemicals on Good Laboratory Practice (GLP). At present, thirty-four (34) OECD countries and six (6) non-member countries i.e. Argentina, Brazil, India, Malaysia, Singapore and South Africa adhere to the system.

NPCB had been designated as the Malaysian Compliance Monitoring Authorities (CMAs) by the Malaysian Government. NPCB is the CMA for the non-clinical safety testing of test items contained in pharmaceutical products, cosmetics products, veterinary drugs and food additives.

A party interested in conducting a clinical trial here in Malaysia would be able to retrieve up to date comprehensive information from their official portal (bpfk.moh.gov.my). Stakeholders are continuously engaged in the guidance and the updates being rolled out by the NPCB itself.

3.1 Regulatory Guidelines

There are key guidelines for conducting clinical trials in Malaysia.

- Malaysian Guidelines for Good Clinical Practice
- The Malaysian Guideline for Application of Clinical Trial Import License and Clinical Trial Exemption
- Malaysian Guideline for Safety Reporting of Investigational Products
- Guidelines for Good Clinical Practice (GCP) Inspection
- Malaysia Guideline for Bioequivalence Inspection

3.2 CTIL/CTX Application Process

3.2.1 Overview

Before commencing any clinical trial involving product(s) that requires CTIL/ CTX and prior importation/ manufacturing product locally for the study, the investigator/ sponsor shall submit application for CTIL/ CTX to NPCB. The following products will require a CTIL/ CTX:

- A product including placebo which is not registered with the DCA and are intended to be imported for clinical trial purpose.
- A product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form and when used for unapproved indication/ when use to gain further information about an approved use for clinical trial purpose.
- A traditional product with a marketing authorization with indication for "traditionally used" when used for unapproved indication/ therapeutic claims for clinical trial purpose.
- An unregistered product including placebo manufactured locally for the purpose of the clinical trial.

3.2.2 Malaysian Guideline for Application of CTIL and CTX is the key guidance for application of CTIL and CTX. Documents to be submitted in a new application for CTIL and CTX are covered thoroughly in the guideline.

3.2.3 Application forms for CTIL and CTX are also available on the NPCB official portal.

3.2.4 Application for CTIL and CTX can be done by an investigator or an authorized person from a locally registered pharmaceutical company/ sponsor/CRO with a permanent address in Malaysia. However, note that the application for CTIL/CTX containing a poison or drug should be made by a Poison License Type A holder for pharmacist in the private sector or an Annual Retention Certificate (ARC) holder for public pharmacist. A letter of authorisation is required if the party conducting the clinical trial in Malaysia is authorising a CTIL/CTX holder to act on behalf and be responsible for all matters pertaining to the CTIL/CTX.

3.2.5 The applicant is responsible for:

- The product and all information supplied in support of his/ her CTIL/ CTX application for his/ her product. He/ she shall be responsible for updating any information relevant to the product or application.
- In case where the applicant is not the manufacturer and where confidentiality prevents disclosure of certain information to the applicant, such information may be furnished to the DCA through the applicant in a sealed envelope marked 'CONFIDENTIAL'.
- Any person who knowingly supplies any false or misleading information in connection with his/ her application for CTIL/ CTX commits an offence under regulation 13 (4), CDCR 1984.

3.2.6 For CTIL application, a face to face appointment is made for the submission of the CTIL dossier. At this meeting the submitted documents go through a review for completeness of document submitted. For CTX application, on the other hand, can be submitted either via post or in person to Centre for Investigational New Product.

3.2.7 After Ethics Committee approval is obtained, the applicant must provide the approval letter to NPCB in order for NPCB to issue the regulatory approval.

CTIL/CTX will only be issued when the approval is granted by both the DCA and ethics committee. However, NPCB will only accept approval granted by IEC/IRB that is registered with the DCA. These Ethics Committees (ECs) within the list are the only ones accepted for NPCB in the issuance of the CTIL/ CTX and the Regulatory Approval Letters. The list of IEC registered with DCA will be reviewed on an on-going basis and should be checked on the NPCB website for the latest list of IEC/IRB Registered with the DCA.

3.2.8 Regulatory approval consists of 2 documents:

- CTIL and/or CTX. There will be a CTIL and/ or CTX for each unique investigational study drug. Each CTIL/ CTX has an expiry date of 3 years.

- Regulatory approval letter. This will stipulate the sites involved and the approved quantity to be imported for each study drug per site. It is recommended that thequantities are calculated based on the planned kit shipments and not per unique investigational study drug to ease the tracking of the imported quantities against the approved quantity. The regulatory approval letter is for the duration of the study. However, as mentioned above, when there are variations throughout the study conduct, appropriate submissions need to be done, as detailed in the aforementioned guideline.

3.3 Documents Required for CTIL/CTX Submission

3.3.1 The documents to be submitted for a new application for CTIL/CTX are stipulated in detail in the Malaysian Guideline for Application of CTIL and CTX. It is strongly recommended that the Guideline be reviewed in detail and referred to during the preparation of the documents required for the Initial Submission, for the Variation of Application and Other Reporting Requirement as well.

3.3.2 The CTIL/CTX Submission Dossier for a new application for CTIL/CTX would comprise of the following main documents:

1. Table of Contents
2. Cover Letter
3. CTIL/CTX Application form
   - Application forms for CTIL and CTX can be downloaded from the NPCB website.
4. Processing fee
5. Company Registration Certificate
6. Applicant's Poison Licence Type A for pharmacist in private sector or ARC for public pharmacist (where applicable)
7. Letter of Authorisation
8. Copy of the opinion of the EC (which is/are registered with DCA)
9. Clinical Trial Protocol
10. Declaration by Investigator/PI
    - The format of the document can be found within the Guideline. Do take note that the original copy of this declaration is to be provided.
11. GCP Certificate and Curriculum Vitae (CV) for Investigator/PI of each trial site
    - Do take note that the GCP Course should be recognised/approved by NCCR, MOH, Malaysia.
12. Informed Consent Form (ICF)
    - The ICF provided can be in English or Bahasa Melayu. The initial version of ICF must be provided during submission. However, a copy of the EC approved ICF version must be submitted together with the EC approval.
13. Pharmaceutical data for all products that require CTIL/CTX
    - Further guidance on the data to be provided is within the appendices within the guidelines.

- Shelf life is based on the available stability data. The applicant should ensure that the stability data submitted is sufficient for the proposed shelf life.

14. Label for all products that require CTIL/CTX
    - Labelling requirements for primary and secondary packaging are stipulated within the appendix of the guideline.
15. Current copy of Certificate of GMP Compliance for the manufacturer and repacker should be submitted
    - There are specific requirements for the GMP certificate. The applicant should ensure the GMP certificates fit the requirements stipulated within the guidelines.
16. Investigator's Brochure
17. Overall risk and benefit assessment
18. Other or additional documents
    - Any other trial related documents that could be relevant for the review of the clinical trial application by DCA, may be submitted, e.g. published clinical data, if applicable.

3.3.3 The applicant/license holder shall inform the DCA of any changes in information received by him/her that cast doubt on the continued validity of the data which was submitted with or in connection with the application for the CTIL/CTX. DCA may also request for supplementary data and/or additional documents, including GLP certification and GLP final report, for application of CTIL/CTX, where necessary.

3.4 Safety Reporting Procedures and Requirements

3.4.1 Malaysian Guideline for Safety Reporting of Investigational Products is the key guidance for safety reporting requirements in Malaysia. The guideline is clear and it covers the reporting process as well.

3.4.2 All Adverse Drug Reactions (ADRs) that are both serious and unexpected are subjected to expedite reporting. This applies to reports from all clinical trials at Malaysia that require CTIL and/or CTX.

3.4.3 The reporting of serious, unexpected adverse drug reactions shall commence from the date of notification of CTIL and/or CTX approval from NPCB for the product used in the trial in Malaysia. This reporting requirement continues until all the sites in Malaysia are closed. The expedited safety reports should be submitted electronically to the NPCB. Details are further detailed in the Malaysian Guideline for Safety Reporting of Investigational Products.

3.4.4 Reporting timeframes

- Fatal or Life-Threatening Unexpected ADRs: The NPCB should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor of a qualifying case, followed by a report as complete as possible within 8 additional calendar days.

- All Other Serious, Unexpected ADRs: The NPCB should be notified as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that a case meets the minimum criteria for expedited reporting.

3.4.5 GCP Inspection

- The first version of Guidelines for Good Clinical Practice Inspection was issued in 2010. The Drug Control Authority (DCA) had endorsed the Guidelines for Good Clinical Practice Inspection in accordance with regulation 29 under Control of Drugs and Cosmetics Regulation 1984 in the 221st meeting on the 29th October 2009. The Guidelines for Good Clinical Practice Inspection will integrate the principles of GCP as described in the Malaysian Guidelines for Good Clinical Practice regulations.

- Inspections can be a triggered or a routine inspection.

- NPCB will notify the applicant not less than 2 weeks before a planned inspection except for triggered inspections. After the inspection, a report will be issued in which the inspected party must respond to the observations with corrective actions/and preventive actions by the stated dateline. The report would then be reviewed internally through the Committee for Inspection and Evaluation of Premises (CIEP) and these final reports with the response and the recommendations by the CIEP would be then tabled to DCA for a decision.

- Classification used for inspection observations are Critical, Major and Minor, for which definitions and possible consequences are detailed in the Guideline as well.

4 IRB/IEC

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects. (Malaysia GCP 3.1.1)

It is the responsibility of the investigator and/or institution where the medical research is to be conducted, to apply via the Principal Investigator (PI) or Corresponding Principal Investigator (for studies with more than one MOH site) to the MREC to seek approval for the conduct of a proposed medical research by the investigator. The investigator and/or institution may delegate the responsibility for MREC submission to the sponsor or sponsor's representative, but the ultimate responsibility for the integrity of the submission always resides with the investigator and/or institution.

4.1 Types of IRB/IEC

In Malaysia, submission to Ethics Committee and National Pharmaceutical Control Bureau (NPCB) can be done in parallel. There are 2 types of Ethics Committees:

Central Ethics Committee: A Central Ethics Committee called the Medical Research and Ethics Committee (MREC), reviews and approves all clinical trials to be conducted at all MOH hospitals as well as institutions without a Local Ethics Committee.

Local Ethics Committee: Non-MOH hospitals may have their own Ethics Committees. The registered ECs with NPCB is available in the NPCB website. (http://portal.bpfk.gov.my/index.php/guidelines-central)

4.2 IRB/IEC Application Process and Documents Required for IRB/IEC Submission

4.2.1 Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia

4.2.1.1 Submission to Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia

- The application process for the MREC is an on-line submission using the National Medical Research Register (NMRR) website. Users are required to register with the National Medical Research Register (NMRR) website and obtain a user account that can be used for all submissions thereafter. All relevant information is available under the User Manual/Documents section in NMRR website (https://www.nmrr.gov.my).

- NMRR is a web based tool designed to support the implementation of the National Institute of Health (NIH) guidelines on the conduct of research in the Ministry of Health Malaysia (MOH). NMRR enables online research registration and online submission, as well as ethical review and approval of MOH research.

- Before the submission process is started, the Corresponding Principal Investigator (for studies with more than one MOH site) needs to be appointed to act as the main investigator in the study. The Corresponding Principal Investigator/ a designated Corresponding Person is responsible in submitting the relevant study documents in NMRR.

- As per the NIH Guidelines for Conducting Research in Ministry of Health Institutions and Facilities (October 2015), if the study registered is an Investigator Initiated Research and does not involve international collaboration, the study would be reviewed by a research review panel prior to MREC's review.

- Studies that are forwarded to MREC are initially accessed to determine the type of review. In the case of clinical research, most of the studies would need to undergo MREC full-board review.

- The PI or Corresponding Principal Investigator is no longer required to attend MREC full-board review meetings unless specific requests are made by the MREC reviewers. If needed, the Secretariat will be communicating with the PI or Correspondence Principal Investigator at least 2 working days prior to the meeting. If the PI or Corresponding Principal Investigator is unable to attend, the Secretariat would make arrangements for SKYPE/teleconference.

- The PI or Corresponding Principal Investigator is no longer required to attend MREC full-board review meetings unless specific requests are made by the MREC reviewers. If needed, the Secretariat will be communicating with the PI or Correspondence Principal Investigator at least 2 working days prior to the meeting. If the PI or Corresponding Principal Investigator is unable to attend, the Secretariat would make arrangements for SKYPE/teleconference.

- The PI or Corresponding Principal Investigator will be informed on the decision within 10 working days after the meeting. Should there be a delay (due to the need for added review/clarifications after the meeting); the MREC Secretary will be communicating with the PI or Corresponding Principal Investigator on the matter.

- The scheduled panel meeting dates are published on the NMRR website. In general, MREC meetings are on the 2nd and 4th Tuesday of each month. The cut-off date (the date study package is forwarded to MREC) is 10 working days before the meeting date.

- Please refer to the User Manual/Documents in the NMRR website for:
  - Investigator Registration-New User Account Creation (this is to briefly explain how to create a user account in NMRR).
  - Step by Step- Research Registration & Submission using NMRR (this is a comprehensive guide to demonstrate how to navigate and complete submission in NMRR).

4.2.1.2 Work Process and Documents Required for MREC Submission Initial

Submission for MREC

Document for Submission	Required?	Comments
Cover letter	Yes	Formal signed cover letter from corresponding PI to Chairperson of MREC (list all investigators and their roles, participating sites and all documents with version number and version date for MREC approval). Cover letter needs to be printed on the hospital letterhead of the Corresponding PI.
Protocol	Yes	To be submitted in English Language
Protocol Review Checklist	Refer comments section	Required to be submitted in the case of Investigator Initiated Research that are interventional
Investigator Brochure	Refer comments section	Required to be submitted if there is an investigational product
Patient Information Sheet (PIS) & Informed Consent Form (ICF)	Yes	Required to submit in English & Malay Language. Other languages (Simplified Chinese, Tamil etc) are optional depending on site needs.
Patient Information Sheet (PIS) Review Checklist	Refer comments section	Required to be submitted for interventional research
Patient Materials	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e. English, Malay, Simplified Chinese and Tamil.
Subject recruitment procedures/ Advertisements	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e. English, Malay, Simplified Chinese and Tamil.

Document for Submission	Required?	Comments
Case Report Forms	Yes	
Insurance Certificate	Refer comments section	Required to be submitted if study is industry sponsored.
PI and Sub-Investigator CV	Yes	Required to submit updated CV.
PI and Sub-Investigator GCP Certificate	Yes	Required for clinical research.
Investigator Agreement, Head of Department and Institutional Approval (IA-HOD-IA)	Yes	This is generated from NMRR. To be signed by Investigator, Head of Department and Institutional Director.
Other Documents including documents related to other site staff, professional indemnity or approval by other ECs	No	
Clinical Trial Agreement	No	
Payments to Investigators / Site budget	No	
Payments to Subjects	Yes	Subject travel reimbursement and the amount per visit must be specified in the Patient Information Sheet under the subject reimbursement section.
MREC Meeting Fee (provide details - how much, when & how)	No	Free of charge.

Document for Submission	Required?	Comments
Online or manual submission	Refer comments section	Online submission in NMRR system.
How to check submission status	Refer comments section	Study Investigators/Corresponding Principal Investigator/Corresponding Person is able to monitor study progress in NMRR once the study is forwarded to MREC.
How study team is informed on the study final decision	Refer comments section	MREC decision letter is provided via e-mail to the Corresponding Principal Investigator
Useful guidance documents	Refer comments section	Online Submission: Step by Step- Research Registration & Submission using NMRR (this is a comprehensive guide to demonstrate how to navigate and complete submission in NMRR)
Useful links	Refer comments section	NMRR website www.nmrr.gov.my MREC Website www.nih.gov.my/web/mrec

Subsequent Reporting for MREC

Requirement	How to Report	Timeline for submission/ reporting	Timeline for submission/ reporting	Comments
Amendments (Amendments in the study documents/ Useful links study team/ study sites)	Please refer to the User Manual/ Documents in the NMRR website for:		*Substantial Amendments:* 20 Working days	Please complete and submit together the

Requirement	How to Report	Timeline for submission/ reporting	Timeline for submission/ reporting	Comments
	√ Step by Step – Request for Amendments		*Non-Substantial Amendments:* 10 Working days	MREC specific form for study amendment **Amendment Application Form** Decision whether the amendment submitted is substantial/ non-substantial will be decided by MREC. MREC decision letter is provided via e-mail to the Corresponding Principal Investigator.
Ethical Renewal	Please refer to the User Manual/ Documents in the NMRR website for: √ Annual Renewal Guide	Submitted at least 2 months prior to the approval lapse date. (For details on MREC approval expiry date, please refer to the MREC Initial Approval letter OR	Within 30 days	Please use the MREC specific form for ethical renewal- **Continuing Review Form** MREC decision letter is provided via e-mail to the

Requirement	How to Report	Timeline for submission/ reporting	Timeline for submission/ reporting	Comments
		MREC Ethical Renewal letter).		Corresponding Principal Investigator
Study Closure/ Termination	Please refer to the User Manual/ Documents in the NMRR website for: √ Study Closure Guide	Study Final Report is submitted via NMRR within two (2) months from study completion. Study Termination Memorandum is submitted via NMRR within one (1) month from study termination.	10 working days	The Study Final Report is submitted when the study has been closed in all the MREC approved sites. The Study Termination Memorandum is submitted when the study is terminated prior to completion. Please use the MREC specific form for: Study Closure- **Study Final Report**

Requirement	How to Report	Timeline for submission/ reporting	Timeline for submission/ reporting	Comments
				Study Termination- **Study Termination Memorandum** MREC decision letter is provided via e-mail to the Corresponding Principal Investigator
Notification for Protocol Deviation (PD	Please refer to the User Manual/ Documents in the NMRR website for: √ Document Submission Guideline	Immediately upon awareness of incident	Immediate acknowledgement e-mail from NMRR to Study Corresponding Person/Corresponding Back-up person.	Please use the MREC specific form for PD reporting (MREC Protocol Deviation/ Violation Report). Each incident requires an individual report to be submitted.

Requirement	How to Report	Timeline for submission/ reporting	Timeline for submission/ reporting	Comments
Other Notifications (Interim Reports, Site Closure notification, etc.)	Please refer to the User Manual/ Documents in the NMRR website for: √ Document Submission Guideline		Immediate acknowledgement e-mail from NMRR to Study Corresponding Person/Corresponding Back-up person.	Up to 8 different documents could be uploaded at a single submission and multiple submissions could be made to MREC at any given time.

4.2.2 Medical Research Ethics Committee (MREC), University of Malaya Medical Centre (UMMC)

4.2.2.1 Submission to Medical Research Ethics Committee (MREC), University of Malaya Medical Centre (UMMC)

- It is the responsibility of the Principal Investigator to obtain approval from MREC before starting the clinical trial/ study. Principal Investigator must ensure that no subject undergoes any trial related procedures before the MREC issues its written approval/favorable opinion for the trial.

- The MREC meets regularly once a month. The submissions must reach the MREC secretariat by the first week of the month and ethics meetings are usually held on the third Wednesday of each month.

- Submission dateline and meeting schedule are available on the UMMC website (http://www.ummc.edu.my/research/research-ethic.asp?).

- The Principal Investigator will be contacted by phone call and email if the study needs to be presented at the MREC meeting.

- For any Interventional Clinical Research, which involves drugs, the principal investigator has to register with the National Medical Research Register (NMRR) https://www.nmrr.gov.my.

- Applications for new studies, amendments, notifications, etc. shall be done via online system in:-
  - Staff Portal - MyUMMC
  - UMMC e-Services

- Register and apply through online URL as below:
  - http://my.ummc.edu.my – for UMMC/UM Faculty of Medicine staff whom have Single Sign On (SSO) login (e-Service i Research).
  - https://eservices.ummc.edu.my - for UMMC/UM Faculty of Medicine staff who do not have SSO login.

- The review timeline for MREC's first decision on a new study is within 1 month from receipt of application by the Secretariat.

- For amendments, notifications or other revisions to an approved study, the review timeline is within 1 month from the date of receipt by the secretariat.

- The following events require prompt reporting to MREC:
  - Deviations from or changes to the protocol to eliminate immediate hazards to the trial subjects.
  - Changes or observations (including SAEs) that increase the risk to subjects and / or affect significantly the conduct of the trial.
  - New information that may adversely affect the safety of the subjects or the conduct of the trial.
  - Any trial, which is prematurely suspended or terminated.

4.2.2.2 Work Process and Documents Required for MREC Submission, University of Malaya Medical Centre (UMMC)

Initial Submission to MREC UMMC

Document for Submission	Required?	Comments
Cover letter	Yes	
Application Form	Online submission	MREC Initial Submission MyUMMC Portal/UMMC eservices
Protocol	Yes	English only.
Protocol Signature Page	No	
Investigator Brochure	Yes	English only.
Informed Consent Form (ICF) and Patient Materials	Yes	Required to submit in English, Malay and Simplified Chinese. Tamil is optional, and not required to be submitted if PI confirms that the study population would NOT require Tamil.
Subject recruitment procedures/ advertisements	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e. English, Malay, Simplified Chinese and Tamil.
Case Report Forms	No	
Insurance Certificate	Yes	
PI CV	Yes	
Sub-Investigator CV	Yes	
PI and Sub-Investigator GCP Certificate	Yes	

Document for Submission	Required?	Comments
Clinical Trial Agreement	Yes	Draft would be sufficient.
Payments to Investigators / Site budget	Yes	Draft would be sufficient.
Payments to Subjects	Yes	Must be specified in the ICF under the subject reimbursement section.
EC Meeting Fee (provide details - how much, when & how).	No	Free of charge.
Online or manual submission	Refer comments section	Online submission by PI/site.
How to check submission status	Refer comments section	Site to check with EC or contact Clinical Investigation Centre for assistance.
Useful guidance documents / links	Refer comments section	http://www.ummc.edu.my/research/research-ethic.asp

Subsequent Reporting

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Amendments	Online Submission. PI/SC to upload relevant documents into submission portal.	PI/SC is able to print out the submission view page once all documents/information is uploaded. Approval letter can be expected within 1 one month (online).	Approval will be provided to Principal Investigator (online).
Notification	Online Submission. PI/SC to upload relevant documents into submission portal.	PI/SC is able to print out the submission view page once all documents/information is uploaded.	All protocol deviations must be reported.
Interim reporting/ progress report/ approval renewal	Online Submission. PI/SC to upload relevant documents into submission portal. Site to complete Annual study report and study closure report form.	PI/SC is able to print out the submission view page once all documents/information is uploaded.	Approval will be provided to Principal Investigator (online).
Completion of clinical trial	Online Submission. PI/SC to upload relevant documents into submission portal. Site to complete Annual study report and study closure report form.	Closure report within one month after the study closure or termination. PI/SC is able to print out the submission view page once all documents/information is uploaded.	

4.2.3 Research Ethics Committee, Universiti Kebangsaan Malaysia (RECUKM)

4.2.3.1 Submission to Research Ethics Committee, Universiti Kebangsaan Malaysia (RECUKM)

- RECUKM is responsible for monitoring the conduct of approved research. In addition to the requirements stated in the approval letter from the RECUKM, the principal investigator shall:
  - Conduct the trial in compliance with the approved protocol.
  - Provide reports of the progress of the trial to the RECUKM, at a frequency directed by the RECUKM (at least annually).
  - Duly notify the RECUKM of any protocol deviation during the conduct of the trial.
  - Notify, in the manner and form specified by the RECUKM, any Serious Adverse Events (SAEs) at any trial sites.
  - Inform the RECUKM as soon as possible of any new safety information from published or unpublished studies, or clinical use that may have an impact on the continued ethical acceptability of the trial.
  - Inform the RECUKM, giving reasons, if the trial is discontinued before the expected date of completion.

4.2.3.2 Work Process and Documents Required for Research Ethics Committee, Universiti Kebangsaan Malaysia (RECUKM)

Initial Submission

Document for Submission	Required?	Comments
Cover letter	Yes	In English.
Application Form	Refer comments section	1.UKM-SPPI- BO01 (Application Form) 2.UKM-SPPI-BO02 (Screening Form) 3.UKM-SPPI-BO04 (Publication Policy Form) 4.Summary of Proposal 5.Documents Acceptance Checklist
Protocol	Yes	English Only.
Protocol Signature Page	No	
Investigator Brochure	Yes	English Only.
Informed Consent Form (ICF) and Patient Materials	Yes	Required to submit in English, Malay and Simplified Chinese. Tamil is optional, and will not be required to be submitted if PI confirms that the study population would NOT require Tamil.
Subject recruitment procedures/ advertisements	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e. English, Malay, Simplified Chinese and Tamil.
Case Report Forms	Yes	
Insurance Certificate	Yes	
PI CV	Yes	
Sub-Investigator CV	Yes	
PI and Sub-Investigator GCP Certificate	Yes	

Document for Submission	Required?	Comments
Other Documents Required, including documents related to other site staff, physician indemnity or insurance etc.	Refer comments section	(1) Summary of proposal (2)Document Acceptance Checklist
Site contracts with sponsor	Yes	Draft Contract is sufficient.
Payments to Investigators / Site budget	Yes	Draft Budget is sufficient.
Payments to Subjects	Yes	Need to be mentioned in the ICF.
Slides presentation (10 slides) about the study	Yes	
Online or manual submission	Refer comments section	Manual submission: Required 1 copy for EC, 1 copy for PI. Submission of softcopy via email to Mrs. Rohaida Md Isa for review and verification first. Once approved, prepare the hardcopy and send to Sekretariat Penyelidikan Perubatan & Inovasi (SPPI), PPUKM. Primary reviewer will then review the contents and issue any queries if applicable prior to the scheduled EC meetings. PI may provide responses to the queries prior to the meeting.
How to check submission status	Refer comments section	Investigator to contact EC officers. EC will provide the decision in writing, which will outline the necessary changes for proposals requiring modifications, usually within ten (10) working days of the scheduled meeting.
Key contacts	Refer comments section	For the application from Faculty of Medicine UKM, all softcopies of study documents should be sent by email to Mrs. Rohaida Md Isa for review: Contact information as below and typically it takes no more than one week for the review and response.

Document for Submission	Required?	Comments
		For Initial submission: Puan Rohaida Binti Md Isa Email: rohaida@ppukm.ukm.edu.my Once approved by Pn Rohaida, site to prepare the hardcopy and send to PPUKM EC, Sekretariat Penyelidikan Perubatan & Inovasi (SPPI). Address: Sekretariat Penyelidikan Perubatan & Inovasi Tingkat 15, Blok Pra-Klinikal , Pusat Perubatan Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras Kuala Lumpur Present in EC Meeting:- 1. Ms. Fatimah Binti Mat Zin Email : fatimahz@ppukm.ukm.edu.my c.c to sepukm@ukm.edu.my • Inquiries regarding the EC meeting. • Status of proposal after EC meeting. • Amendment submission for EC meeting. • Amendment submission after EC meeting 2. Ms. Nurul Nadiah Binti Isahak Email : nurulnadiah@ppukm.ukm.edu.my c.c to sepukm@ukm.edu.my • Amendment/update after EC approval. • Notification • Interim reporting/Progress report • SAE/SUSAR Reporting

Document for Submission	Required?	Comments
		Address: Sekretariat Etika Penyelidikan UKM, Tingkat 1, Blok Klinikal, Pusat Perubatan Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000, Cheras Kuala Lumpur
Useful guidance documents / links	Refer comments section	http://www.ppukm.ukm.my/sppi/muat-turun-borang-penyelidikan/

Subsequent Reporting

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Amendments	1. Prepare EC submission Cover letter 2. To submit soft copy of amendments along with signed cover letter via email first to Ms. Fatimah Mat Zin and prepare 1 hardcopy for manual Submission to EC.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier.	Approval will be provided to Principal Investigator.
Notification	Site to send 1 submission dossier (hard copy) to EC.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier.	All protocol deviations are required to be reported

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Interim reporting/ progress report/ approval renewal	All softcopies of documents should be emailed to Mrs. Rohaida Md Isa and c.c to Ms. Nurul Nadiah Isahak. Once the application is verified as complete, 1 set of hardcopy application must be submitted to Secretariat of Medical Research & Innovation, PPUKM (SPPI) and Chairman of Research Ethics Committee UKM. Submit cover letter with the completed UKM-SPPI-BO09 Progress Report Form Research Performance_03 Nov 2014.	Every 6 months, for the duration of the study. Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier. Annual reports and requests for renewals must be sent to the RECUKM thirty (30) days prior to the expiry date of the letter of ethics approval.	
Completion of clinical trial	All softcopies of documents should be emailed to Mrs. Rohaida Md Isa and c.c to Ms. Nurul Nadiah Isahak. Once the application is verified as complete, 1 set of hardcopy application must be submitted to Secretariat of Medical Research & Innovation, PPUKM (SPPI) and Chairman of Research	Principal Investigator to provide RECUKM with a final report within 30 days of the expiry date of the letter of ethics approval.	

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
	Ethics Committee UKM. Submit cover letter with the completed UKM-SPPI-BO10 RESEARCH FINAL REPORT FORM_03 Nov 2014		

4.2.4 Human Research Ethics Committee, Universiti Sains Malaysia (JEPeM)

4.2.4.1 Submission to Human Research Ethics Committee, Universiti Sains Malaysia (JEPeM)

- An application for review or for ethical approval to JEPeM-USM should be submitted by a Principal Investigator responsible for the ethical and scientific conduct of the research.

- Application should be submitted in the prescribed application form (JEPeM-USM FORM 2 (B) 2015: Registration and Application Form) to the JEPeM-USM secretariat office according to the classification of PI.

- Applicants should submit fifteen (15) copies (including one original copy) of the application forms and all the relevant documents.

- Complete application shall be considered for review in the coming JEPeM-USM meeting not more than twenty-five (25) working days upon receipt by the Secretariat.

- The Secretariat will acknowledge the receipt of a complete application. Incomplete application will be returned back to the applicant.

- The Secretariat will verify the completeness of the application based on JEPeM-USM FORM 2(A) 2015 Review Checklist.

- Tentative dates of JEPeM's meetings are available on the JEPeM website (http://www.jepem.kk.usm.my). In general, JEPeM has 2 meetings a month.

4.2.4.2 Work Process and Documents Required for Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM)

Initial Submission

Document for Submission	Required?	Comments
Cover letter	Yes	In English.
Application Form	Refer comments section	1. JEPEM USM Form 2A 2015 Review Checklist_7Sept2015 2. JEPEM USM Form 2B 2015 Registration and ApplicationForm_7Sept2015 3. JEPEM USM Form 2(C)(i) 2015 Study Protocol Assessment _ interventional study or JEPEM USM Form 2(C)(ii) 2015 Study Protocol Assessment_non-interventional study 4. JEPEM USM Form 2(D)(i) 2015 Informed Consent Assessment Form_interventional or JEPEM USM Form 2(D)(ii) 2015 Informed Consent Assessment Form_non-interventional
Protocol	Yes	English Only.
Protocol Signature Page	Yes	
Investigator Brochure	Yes	English Only.
Informed Consent Form (ICF) and Patient Materials	Yes	Required to submit in English, Malay and Simplified Chinese. Tamil is optional, and will not be required to be submitted if PI confirms that the study population would NOT require Tamil.
Subject recruitment procedures/ advertisements	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e. English, Malay, Simplified Chinese and Tamil.
Case Report Forms	Refer comments section	Optional

Document for Submission	Required?	Comments
Insurance Certificate	Yes	
PI CV	Yes	
Sub-Investigator CV	Yes	
PI and Sub-Investigator GCP Certificate	Yes	
Other Documents Required, including documents related to other site staff, physician indemnity or insurance etc.	Yes (if applicable)	
Site contracts with sponsor		Draft Contract is sufficient.
Payments to Investigators / Site budget	Yes	Draft Budget is sufficient.
Payments to Subjects	Yes	No need to mention in the ICF. In order to keep the participation really voluntary, the PI needs to mention the honorarium but only after participant have signed the consent form. Once the participant agreed and signed the consent form, all the details about the honorarium including amount, how and when the payment will be made is available in the separate sheet of documents
Online or manual submission	Refer comments section	Manual submission.
How to check submission status	Refer comments section	Investigator to contact EC officers.

Document for Submission	Required?	Comments
Key contacts	Refer comments section	Mr. Mohd. Bazlan Hafidz Mukrim Secretary of Human Research Ethics Committee USM Centre for Research Initiatives, Clinical & Health Sciences USM Health Campus Tel. No. : 09-767 2354 / 09-767 2352 Email : jepem@usm.my
Useful guidance documents / links	Refer comments section	http://www.jepem.kk.usm.my/

Subsequent Submission

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Amendments	1. Complete JEPEM-USM FORM 3(A) 2015 Study Protocol Amendment Submission Form 2. Manual Submission, 15 copies to EC and 1 copy for PI reference. Courier the hard copies of submission dossier to EC. 3.Full board review for amendment that (may include but is not limited to): -Additional treatments or the deletion of treatments -Any changes in inclusion/exclusion criteria	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier.	Approval will be provided to Principal Investigator.

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
	- Change in method of dosage formulation, (e.g. oral changed to intravenous) - Significant change in the number of subjects - Significant decrease or increase in dosage amounts 4. Site to contact EC to check on the approval status.		
Notification	Submit 1 copy of notification letter to EC and EC will acknowledge receipt. Study Protocol Non-compliance (Deviation or Violation) Report. JEPeM-USM FORM 3(D) 2014: Study Non-Compliance Report	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	All protocol deviations are required to be reported
Interim reporting/ progress report	Ethical clearance or approval is typically granted for a period of one (1) year. Continuing review is required to be done once a year. Form 3 (B) 2015: Continuing Review Application	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter. Continuing Review Application Form 3	The frequency of continuing review is indicated in the Study Protocol Approval Letter.

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
		(B) 2015 to be submitted 60 days prior to expiry date.	Approval will be provided to Principal Investigator.
Completion of clinical trial	Final Report Form for Interventional Study. JEPeM-USM FORM 3(C) (i) 2014 for Interventional Study	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	
Early Study Termination	Early Study Termination Application Form. JEPeM-USM FORM 3E2015	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	Approval of this application would require further completion of JEPeM-USM FORM 3(C) 2014: Final Report Form

4.2.5 Joint Penang Independent Ethics Committee (JPEC)

4.2.5.1 Submission to Joint Penang Independent Ethics Committee (JPEC)

- JPEC or Joint Penang Independent Ethics Committee is a 13-member committee formed under the joint authority of the Penang Medical College and Gleneagles Clinical Research Centre, Penang and other private medical institutions. JPEC conducts initial and continuing ethical review of clinical trials conducted.

- JPEC is unique in that while most ethics committees are institutional i.e. formed by and comprising members from one particular institution, JPEC unites members from the private and public medical centers and institutions in Penang, Malaysia.

- JPEC meets regularly once a month and submissions need to be made at least 2 weeks before a planned meeting. Refer to EC meeting schedule posted on: http://info-kinetics.com/jpec/jpec-meeting-dates. Applicants will be notified of the date and time of the JPEC meeting (at least 7 days in advance) where the application is to be reviewed. The investigator will be required to attend this meeting to answer queries from JPEC members.

4.2.5.2 Work Process and Documents Required for Joint Penang Independent Ethics Committee (JPEC)

Initial Submission

Document for Submission	Required?	Comments
Cover letter	Yes	In English.
Application Form	Refer comments section	1. Application Form To Conduct A New Research Project Involving Human Subjects (FOM-JPEC-15008) 2. Applicant's Document Checklist for Submitting an Application to Conduct A New Research Project 3. If tissues/samples will be used for genetic study, a separate checklist, i.e. FOM-CLN-07021-additional checklist for research projects involving genetic tests" will need to be completed and submitted.
Protocol	Yes	English only.
Protocol Signature Page	No	
Investigator Brochure	Yes	English Only.
Informed Consent Form (ICF) and Patient Materials	Yes	1. Required in English, Malay, Simplified Chinese and Tamil (if applicable). 2. Translation Cert or Translation Validation Form (TVF) is required to be submitted for each translated documents. The ICF will need to fulfil all the elements listed in the "applicant's checklist of minimum requirements in the informed consent form and written subject information".
Subject recruitment procedures/ advertisements	Refer comments section	Not mandatory, submit if applicable. To be submitted in applicable languages, i.e.

Document for Submission	Required?	Comments
		English, Malay, Simplified Chinese and Tamil.
Case Report Forms	Refer comments section	
Insurance Certificate	Yes	
PI CV	Yes	
Sub-Investigator CV	Yes	
PI and Sub-Investigator GCP Certificate	Yes	
Other Documents Required, including documents related to other site staff, physician indemnity or insurance etc.	Yes	Indemnity letter indemnifying JPEC
Site contracts with sponsor	Not applicable	
Payments to Investigators / Site budget	Yes	
Payments to Subjects	Yes	Need to be mentioned in the ICF.
Online or manual submission	Refer comments section	Manual submission. Submission requires 13 copies (1 original and 12 photocopies) of the completed application forms with supporting documents to JPEC Secretariat. A one-time application fee of RM 2000 per research project is charged for the services of JPEC to review sponsored research. However, it is the prerogative of JPEC to waive this fee for non-commercial and non-sponsored research.

Document for Submission	Required?	Comments
		No further fees are charged for reviewing applications for amendments to research projects already approved by JPEC or for review of progress, serious adverse event and closure reports.
How to check submission status	Refer comments section	Investigator to contact EC officers.
Key contacts	Refer comments section	JPEC Secretariat, C/o Gleneagles Clinical Research Centre 5th floor, Gleneagles Medical Centre, 1 Jln. Pangkor, 10040 Penang. Phone number: +604-2285760 or +604-2229111 ext.9503 or 9502; Fax number: +604-2285715.
Useful guidance documents / links	Refer comments section	http://info-kinetics.com/jpec

Subsequent Submission

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Amendments	All amendments are required to be submitted with the use of a specific application form: FOM-JPEC-15010 Application for Amendment to Research Project Involving Human Subjects. For applications, that may affect subject safety, rights or welfare, the proposed	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier.	

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
	amendments and study documents(s) with proposed amendments clearly indicated (tracked changes) and the rationale for the amendment needs to be submitted along the with the form.		
Notification	Sometimes minor administrative amendments are submitted to JPEC for its information only.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	Protocol Deviations to be submitted as notification via a cover letter with enclosed PD report.
Interim reporting/ progress report	A research project progress report is to be submitted to JPEC at specified intervals (usually annually) once a trial is ongoing. Normally, the first research project progress report is due one year from the date of issue of the JPEC Decision Notification Form. However, studies with higher risk to subjects may require more frequent progress reporting. For progress report, the form to be completed is FOM-JPEC-15012: Research-Project-Progress-Report-Form.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	Investigator(s) involved in ongoing trial(s) are required to submit to JPEC their most recent, updated curriculum vitae and Annual Practicing Certificate annually (beginning of each year) until JPEC is notified of study or site closure.

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Completion of clinical trial	Upon study closure, a research project closure report is to be submitted to JPEC. The form to be completed is FOM-JPEC-15013: Research-Project-Closure-Report-Form.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	
Early Study Termination	Site to submit FOM-JPEC-15013: Research-Project-Closure-Report-Form.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the letter.	

4.2.6 Research Ethics Committee (REC), Universiti Teknologi Mara (UiTM)

4.2.6.1 Submission to Research Ethics Committee (REC), Universiti Teknologi Mara (UiTM)

- The Research Ethics Committee (REC) of Universiti Teknologi MARA (UiTM) was established and approved by the Vice Chancellor of UiTM in 2004. The REC is currently managed by the Research Management Centre at the Institute of Research Management and Innovation (IRMI). The REC consists of 19 members from UiTM, other academic institutions and also from the public. Meetings are held on the third Tuesday every month.

- All research proposals involving human subjects in UiTM must be approved by the Faculty's Research Committee and UiTM REC prior to the start of research. When the research involves using facilities of the Ministry of Health (MOH), researchers should obtain the approval from the Medical and Research Ethics Committee (MREC) of the MOH.

4.2.6.2 Work Process and Documents Required for Research Ethics Committee (REC), Universiti Teknologi Mara (UiTM)

Initial Submission

Document for Submission	Required?	Comments
Cover letter	Yes	
Application Form	Refer comments section	1. Application Form for Ethics Approval (Borang REC 1/ 2016 Rev 1) 2. PART E - ETHICAL QUESTIONNAIRE (Borang REC 1E / 2016) 3. Checklist for Applicants for site to fill out (Borang REC 4/2016)
Protocol	Yes	English only.
Protocol Signature Page	No	
Investigator Brochure	Yes	English Only.
Informed Consent Form (ICF) and Patient Materials	Yes	Required to submit in English and Malay. Simplified Chinese and Tamil are optional, and will not be required to be submitted if PI confirms that the study population would NOT require Chinese and Tamil. (UiTM Template for subject information sheet and consent form-Borang REC2/2016 BM and BI)
Subject recruitment procedures/ advertisements	No	
Case Report Forms	Yes	
Insurance Certificate	Yes	
PI CV	Yes	
Sub-Investigator CV	Yes	
PI and Sub-Investigator GCP	Yes	

Document for Submission	Required?	Comments
Certificate		
Other Documents Required, including documents related to other site staff, physician indemnity or insurance etc	Not applicable	
Site contracts with sponsor	Yes	
Payments to Investigators / Site budget	Yes	
Payments to Subjects	Yes	Need to be mentioned in the ICF.
Online or manual submission	Refer comments section	Manual submission For Initial Submission to Faculty of Medicine (Selayang or Sg Buloh Campus) 1. Investigator to prepare 10 hard copy submission dossiers + 1 CD-ROM. (secretariat only need 1 copy) 2. Investigator to submit to Research Secretariat in UiTM Sg Buloh for the Research Committee Meeting by the Faculty of Medicine (Faculty Meeting will be held every 2nd week of Tuesday). 3. Once approved by Chairman of the Research Committee in the Faculty of Medicine , they will help to submit to the Secretariat for REC in UiTM Shah Alam. (REC meeting held once a month, calendar available online on their website) 4. Decision of submission within one month.

Document for Submission	Required?	Comments
How to check submission status	Refer comments section	Investigator to contact the Secretariat for REC.
Key contacts	Refer comments section	http://uitmethics.uitm.edu.my/v1/index.php/contact-us
Useful guidance documents / links	Refer comments section	http://uitmethics.uitm.edu.my/v1/index.php

Subsequent Submission

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Amendments	Send 1 amendment submission dossier (hard copy and soft copy) to the REC Secretariat.	Site to make a copy of the cover letter and obtain an acknowledgement stamp when submitting the dossier. Submission should be made 2 weeks prior to the REC meeting. Decision will be given within 2 weeks after the REC meeting.	Approval will be provided to Principal Investigator.
Notification	Send 1 amendment submission dossier (hard copy and soft copy) to the REC Secretariat.	The Secretariat will fax for notification or get acknowledgement stamp when submitting the dossier.	

Requirement	How to Report	Timeline for submission review/ meeting & approval	Comments
Interim reporting/ progress report/ approval renewal	Send 1 amendment submission dossier (hard copy and soft copy) to the REC Secretariat.	Submission should be made 2 weeks prior to the REC meeting. Decision will be given within 2 weeks after the REC meeting.	Approval will be provided to Principal Investigator.
Completion of clinical trial	Send 1 amendment submission dossier (hard copy and soft copy) to the REC Secretariat.	The Secretariat will fax for notification or get acknowledgement stamp when submitting the dossier.	

4.2.7 Submission to other Local Ethics Committee

The standard EC submission package includes:

- EC Application Form
- Submission Checklist
- Cover Letter
- Study Protocol
- Investigator's Brochure
- Subject Information Sheet and Informed Consent Form in English, Malay, Simplified Chinese and Tamil (if requested), site specific version
- Insurance Certificate + Physician Indemnity Letter (if applicable)
- CV of all investigators + GCP Certificates (if required by EC)
- Any patient related materials (i.e. advertisement, patient diary, etc.)
- Financial contract (if applicable)
- Statement of publication rights (if applicable). This can be obtained from the protocol, usually under Publication Policy

The local EC meeting dates and review differ depending on the number of clinical trials submitted.

4.3 Safety Reporting Procedures and Requirements

4.3.1 Serious Adverse Event (SAE) reporting

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
MREC (involving MREC approved sites)	Initial report as soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.	No later than 15 calendar days from awareness of event by investigator.	MREC Website www.nih.gov.my/web/mrec/timeline Follow up information should be actively sought and submitted to MREC as soon as it becomes available. SAEs involving other Malaysian sites (but not MREC approved sites) need to be reported to MREC but this can be done periodically.
MREC, UMMC	All SAEs have to be reported by the investigator to MREC immediately and not more than 48 hours of notification. A written report on the MREC SAEs form (BK-MIS-1118) is to be submitted promptly and not more than 7 days to MREC.		Medical Ethics Application Standard Operating Procedure (SOP), Section 7.24 (c) http://www.ummc.edu.my/files/ethic/SOP%20edited%2023032015%20onlineversibaru.pdf
The Human Research Ethics Committee of USM (JEPeM)	Immediately		http://www.jepem.kk.usm.my/
UKM REC	***Local serious adverse events:*** A verbal report should be made within 48 hours of event	***Foreign serious adverse events:*** OTHER SAE, reports submitted	Guidelines for Ethical Review of Clinical Research Or Research Involving Human Subjects, Research Ethics Committee (REC), Universiti Kebangsaan Malaysia

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
	occurrence or discovery. A written report should be submitted as soon as possible but no later than seven (7) calendar days upon awareness of the occurrence. An updated written report must be submitted within thirty (30) additional calendar days from the initial notification. Foreign SAEs: ALL FATAL OR LIFE THREATENING SAEs as soon as possible but no later than seven (7) calendar days upon receipt from sponsor or the Contract Research Organization (CRO).	within fifteen (15) calendar days upon receipt from sponsor or the Contract Research Organization (CRO).	

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
JPEC or Joint Penang Independent Ethics Committee	All adverse drug reactions (ADRs), which are both serious and/or unexpected, are to be reported to JPEC. In the case of SAEs occurring in the investigator's institution, the investigator is to notify the JPEC Chairperson within 24 hours of its notification to the investigator, using the JPEC SAE Report.		http://info-kinetics.com/jpec
Sunway Medical Centre Independent Research Ethics Committee (SREC)	Both serious and unexpected occurring in the Sunway Medical Centre is to be reported to SREC within one working day from first knowledge by the investigator or his research team.		http://sunwaymedical.com/wp-content/uploads/2015/11/Form-3-SAE-Report-Form.pdf

4.3.2 Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
MREC (involving MREC approved sites)	Initial report as soon as possible but not later than 7 calendar days from awareness of SUSAR by investigator, followed by a complete report within 8 additional calendar days.	No later than 15 calendar days from awareness of event by investigator.	*MREC Website www.nih.gov.my/web/mrec/timeline* SUSARs involving other Malaysian sites (but not MREC approved sites) needs to be reported to MREC but can be done periodically. Same applies for global SUSARs
MREC, UMMC	As soon as possible but not later than 7 calendar days from awareness of event by investigator, followed by a complete report within 8 additional calendar days.	As soon as possible but no later than 15 calendar days from awareness of event by investigator. Follow up information should be actively sought and submitted as it becomes available.	Medical Ethics Application Standard Operating Procedure (SOP), Section 7.24 (d) http://www.ummc.edu.my/files/ethic/SOP%20edited%2023032015%20onlineversibaru.pdf
	The following foreign SUSAR do not require reporting: i) Clinical Trial not conducted in UMMC. ii) Suspected drug is known to be other than trial drug (e.g. Other treatments, placebo or comparator drug). iii) SAE and not drug related. iv) Suspected Expected Serious Adverse Reaction.		

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
The Human Research Ethics Committee of USM (JEPeM)	Immediately		*http://www.jepem.kk.usm.my/*
UKM REC	Overseas SUSAR: Reports are submitted within thirty (30) calendar days upon receipt from the sponsor or the Contract Research Organization (CRO).		Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects (page 58)
JPEC or Joint Penang Independent Ethics Committee	Investigator is to report (cc. local investigator) the SUSAR to JPEC within 7 calendar days from first knowledge by the investigator. If there is additional information, this should be submitted within 8 calendar days.	Submit to JPEC within 15 calendar days from first knowledge by the investigator.	http://info-kinetics.com/services/jpec For SAEs outside of the investigator's institution (applicable in multicenter trials): a) Only SUSAR are to be submitted to JPEC b) Only protocol specific investigational product(s) SUSARs are to be submitted to JPEC. c) Periodic line listings have to be accompanied with a brief report by Sponsor highlighting main points of concern (if any). d) Annual Safety Report is expected on an annual basis throughout the whole clinical trial course. This report will describe concisely all new safety information relevant for the trial and to assess the safety conditions of subjects in the trial.

Ethics Committee	Fatal / Life Threatening Events	Non-Fatal/ Non-Life Threatening Events	Reference
Sunway Medical Centre Independent Research Ethics Committee (SREC)	SAEs reported outside Sunway Medical Centre (e.g. Those received via CIOMS reports in Multicenter Studies) are to be notified to SREC within one month of its receipt by the Investigator or his/her research team.		http://sunwaymedical.com/wp-content/uploads/2015/11/Form-3-SAE-Report-Form.pdf

5 Other Clinical Trial Requirements

5.1 Study Drug Supplies

- The Certified True Copies of the Clinical Trial Import License (CTIL) and Pharmacist License A are required to be with the clearance vendor at the airport for shipment release.

- It is important to note that within the guidelines, there is a requirement that the CTIL holder shall submit to the DCA the Drug Accountability Report for Importation. This would require the CTIL holder to keep track of the quantities of clinical trial drug that is imported within the country and that it does not exceed the quantity approved by NPCB. The format of this report is indicated within the Malaysian Guideline for Application of CTIL and CTX. It is critical that the shipment quantities are being tracked on an on-going basis and to ensure an application of variation is submitted to obtain additional approved quantities, if needed, ahead of time.

5.2 Biological Samples Importation/Exportation

- Governing Acts and Regulations
  - Prevention and Control of Infectious Disease Act 1988

  - Prevention and Control of Infectious Diseases (Importation and Exportation of Human Remains, Human tissues and Pathogenic Organisms or Substances) Regulations 2006

- The import/export permit can be applied for through an online application using the BLESS system (https://open.bless.gov.my). The applicant needs to complete the online application form and provision the following documents: a copy of NRIC or passport of the applicant, a certification or documentation from the importing or exporting country and information or documentation on method of disposal. There are fees to be paid for the private sectors and the amount depends on the risk group category for the specimens that are being exported.

- An import/export permit for the year will be issued upon approval. The copy of the permit needs to be provided together with the specimens at the time of import/export. The import/export permit needs to be renewed annually.

5.3 Communication Device Importation

- Governing Acts and Regulations for importation of communication equipment.
    - Customs Act 1967 Customs (Prohibition of Imports) Orders 1988
- Communication equipment, which has communication network facilities or customer equipment, which may include fixed and wireless equipment would need to be certified before it can be used, offered for sale or sold. Certification activities for communication equipment are carried out by SIRIM QAS International Sdn. Bhd. (SIRIM QAS), which is a registered certifying agency with the Malaysian Communications and Multimedia Commission (MCMC).
- It is important to note that prior to applying for the import permit online via the e-permit system (http://epermit.dagangnet.com), the importer has to register as an e-permit user with SIRIM QAS International Sdn. Bhd. This can be done via the e-ComM online certification system (http://ecomm.sirim.my). There are also fees associated with the online certification as well as the e-permit.
- For more information on what is required for the application for a permit for communication devices, please do review the FAQ on the MCMC website (http://www.skmm.gov.my/skmmgovmy/files/attachments/FAQ_EqCert_3.pdf)
- SIRIM QAS International Sdn. Bhd. will issue an import permit that has a validity of 3 months.

5.4 Medical Device Importation/Exportation

- Clinical Research on Medical Devices or Medical Devices being used in a Clinical Research has its own separate process and guidelines.

- It is important to know that the Medical Device Authority (www.mdb.gov.my) governs these processes and it is best to reach out to the MDA to further understand the up to date steps in ensuring that the appropriate documentation is in place in importing or exporting medical devices.

6 Clinical Trial Agreement and Study Budget

Clinical trial agreement (CTA) is a legally binding contract that manages the relationship between the parties involves namely sponsor, the institution and principal investigator. It is an important legal document in clinical trial as it documented and formalizes the understanding between the parties and provides a legal and financial terms relating to the performance of a clinical trial.

In Malaysia, CTA and budget related to employees of Ministry of Health (MoH) Malaysia will be endorsed by Clinical Research Malaysia (CRM). CRM is authorized by the Malaysia's government for these purposes representing the clinical research industry in Malaysia. Whereas CTA which involves negotiation with private hospitals and Institute of Higher Learnings (e.g. University Hospitals) usually has their local unit of Clinical Research Centre (CRC) whom will manage, negotiate and finalize contracting.

This includes the clinical trials initiated by the investigators themselves. Investigator Initiated Trials (IIR) may or may not require CTA depending on the procedures involved as well as the category of clinical trials.

CTA is mentioned in ICH-GCP as well as MGCP.

ICH-GCP 1.17: "A contract is a written, dated and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract."

ICH-GCP 4.9.6 & 5.9: "The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator or institution."

MGCP 5.1.4 of the GCP provides that all agreements made by the sponsor with the investigator or any other party in connection with the trial should be in writing, as part of the study protocol or in a separate agreement.

6.1 Clinical Trial Budget

Budget negotiation can be a lengthy and tedious process because each trial has different budget based on the complexity of the clinical trial and the capital of the sponsor. Sometimes, due to insufficient budget, contracting parties could not reach agreement with budget and had to resort to termination of startup of a clinical trial. Also, there could be situation where sponsor faced financial constrain and had to terminate the clinical trial even though it has gone through start up and recruited several subjects.

In general, clinical trial budget should include the following purpose being paid or provided by sponsors:

1. Fair market value of the staff working hours proportionate to the clinical trial conduct.
2. Hospital charges for consumables and equipment if not provided by the sponsor.
3. Overhead charges in percentage or fixed price as specified by the trial site if applicable.
4. Adherence to local taxation system (example GST, VAT etc.). Currently, all services will be subjected to 6% GST implemented by Malaysia Government on 01 April 2015 onwards.
5. Insurance and indemnity for the sponsor's protocol and IPs.

Clinical trial budget can be presented in various methods. The budget can be designed to be paid per subject enrolled, monthly fees or even on milestone achievements. Therefore, it is up to the contracting parties to negotiate the schedule of payment and method of payments. All the payments made payable to site by the sponsor, must be clearly written in the CTA and its terms and condition for payment. Payment made to the site must be made in fair market value and also for only the work done related to the clinical trial.

Compensation to the trial subjects must be handled with caution and reasonable limits so that there will be no undue influence to them. In addition, amount related to subject compensation will need to be approved by the EC. Usually, subject compensation cannot be paid due to loss of wages. This will be specified also in the CTA how much each subject will be paid for transportation or meal allowances. In addition, paid amount will be invoiced by the investigator to the sponsor, where sponsor may request investigator to provide payment records for the subjects for verification purposes.

6.2 Review and negotiation of CTAs

The requirements for reviewing CTAs lie with the contracting parties and their organizations. Sponsors usually have their corporate legal department to ensure all the terms specified in the CTA will be sufficient to adhere to the sponsor's local regulations of conducting clinical trials and the data collected can meet the requirement of their Regulatory Authorities. Whereas for the Investigators and Institutions whom are being engaged by the sponsor to perform clinical trial, they will need to ensure the CTA are adhered to the local governing laws and bodies. Therefore, the negotiation process can be difficult to complete if it is a first working experience for particular Sponsor, Investigator or Institution. The negotiation process may also end with disagreement to certain terms and condition that lead to unsuccessful execution of a CTA.

According to MGCP 5.6.3 provides that the sponsor should obtain the investigator's/ institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirements(s) and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;
(b) To comply with procedures for data recording/reporting;
(c) To permit monitoring, auditing and inspection;
(d) To retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed.

Below are some sections that are generally mentioned in a CTA and what they mean:

1. Definition of the signing parties:
   Sponsor and its affiliates, Investigators legal details and Institution's legal entity are being specified in this section. Usually the contracting parties mentioned will officially sign the CTAs in the signatories section.

2. Study title and Protocol ID:
   Title of the protocol and usually indicates as well to cover its amendments in the life of the clinical trial.

3. Independent Ethics Committee:
   Conditions and requirements of the investigators to follow recommendations of Ethics Committee that review, approve or disapprove the protocol.

4. Trial Conduct:
   Describe how the study will be conducted in accordance to which protocol.

5. Sponsor Drug or Investigational Product (IP):
   Define which drugs are owned by sponsor. Custodian and rights for dispensing, Control and use of IPs are defined as well. In addition, if there is any reimbursement for the IPs or comparator drug will be stated in this section.

6. Research Grant/ Funding:
   Funding or grant that sponsor will agree to pay to Investigator and Institution for conducting the clinical trial.

7. Trial Subject enrollment:
   The agreement of Investigator and Institution to enroll the subject in accordance to the protocol requirements will be defined in this section.

8. Informed Consent:
   Type of consent obtained from the subject that matches the protocol needs.

9. Adverse Event (AE):
   Any compensation and management of AE that sponsor is obligated to provide coverage and what will not be covered by the sponsor, e.g. protocol deviation or negligence.

10. Protected Health Information:
    This section will detail how the subject's health information is protected. Subject identifiers are not to be collected by the sponsor and how the subject's identity is blinded.

11. Confidential information:
    Sponsor will usually define which are the confidential information that the Investigators or Institution should not disclose to the public. How long this confidentiality agreement will last and methods of returning confidential information to the sponsor are also specified here. In addition, the law that governs this section will also be outlined.

12. Trial Data, Biological Samples and Records:
    Ownership of the trial data, medical records, personal information, biological samples and retention of this samples or information will be defined in this section.

13. Inspection and Audits:
    This section defines who will be authorized to perform Inspections and audits for the mentioned clinical trial. In addition, indication of who should be notified if the mentioned trial will be audited by internal or external parties.

14. Inventions:
    What will happen if new inventions or outcome that was generated by the clinical trial.

15. Publications or Publicity:
    Who will have the rights for publications on new findings from the study conduct and also if there is any restriction on using the names for advertising and promotion purposes.

16. Indemnification:
    Sponsor's indemnification, Investigator's indemnification and Institution's indemnification definition will be specified in this section. Exclusions, notification and settlement will be defined according to the applicable laws specified in this section.

17. Terminations:
    Conditions of trial conduct termination are specified in this section. This section also defines who can terminate the study in the specified conditions.

18. Insurance:
    Besides clinical trial insurance by the sponsor, investigator and institution will provide insurance coverage in accordance to local regulations.

19. Debarment, Exclusion, Licensure and Response:
    This is a declaration that the Investigators are not being barred or restricted to conduct clinical trials and have the appropriate license to conduct medical treatment or clinical trials.

20. Governing Law:
    a. International Law
        i. Anti-bribery law
        ii. Personal Data Privacy Act (PDPA)
        iii. Applicable law of the sponsor's country
    b. Country Law
        i. NPCB
        ii. Local or country EC
        iii. MDA
        iv. Cell and genetic engineering
    c. Responsible parties/Sponsor company policy
        i. Subject compensation policy
        ii. Compassionate use of IP policy

Other sections such as assignment and delegation, equipment provided, duration of the obligations and contact methods may also be defined in a clinical trial agreement.

6.3 Government Hospital

Government Hospitals including full service general hospitals and health clinics where the application will be submitted to the MREC for Ethics Committee review. The CTA can be submitted to CRM for their review and endorsement. CRM will provide a unique endorsement code number for each CTA that was reviewed and approved by CRM. For more details, please visit their website http://www.clinicalresearch.my

6.4 University Hospital

For applications submitted to the Research and Ethics Committees of universities or private institutions, the requirement to submit the CTA for review and approval by the said Committees is subject to the specific rules of the university or institution. In most cases, the draft CTA would be one of the documents required to be submitted for approval.

Generally all University hospitals have their own clinical research center that assist in connecting the interested investigators and sponsors to the correct contacts for legal review. Newly established university hospital that may not have this special unit to assist in the clinical trial activities may not have a legal review department. Therefore, they can utilize CRM to assist in legal review of the CTA for them which CRM's CTA template will be preferred.

6.4.1 University Malaya Medical Centre (UMMC)
Institution has own legal counsel for reviewing contracts including CTA. All CTA must go through legal review before execution. (Template is tripartite agreement)
Contact with the legal department for clinical trial can be found in the link below:
Ref: http://www.clinicalinvestigationcentre.com/FAQ
Website: http://www.clinicalinvestigationcentre.com/

6.4.2 UKM Medical Centre (UKMMC)
Institution does not have specific template for CTA. However, their legal counsel must review all CTA before execution. (Template is tripartite agreement)
Contact with the legal department for clinical trial should be done through the Principal Investigator at site.

6.4.3 Hospital University Sains Malaysia (HUSM)
Institution does not have specific template for CTA. However, their legal counsel must review all CTA before execution. (Template is tripartite agreement)
http://www.research.usm.my/

6.4.4 Universiti Teknologi MARA (UiTM)
Institution does not have specific template for CTA. However, their legal counsel must review all CTA before execution. (Template is tripartite agreement)
http://uitmethics.uitm.edu.my/v1/index.php%20

6.4.5 Monash University
Private universities have their own legal counsel to review CTAs. Principal Investigators should be contacted to send in the CTA templates for review. (Template is tripartite agreement)
http://www.med.monash.edu.my/research

6.4.6 University Putra Malaysia (UPM)
No specified legal counsel for reviewing of industry sponsored trials. CRM template can be used and also utilizing CRM for contract review for clinical trials.

6.5 Private Hospital

Each private hospital settings require some legal review of CTA by their board members. Therefore, each listed private hospitals has own procedures for legal review of any CTA templates that the sponsor may present. Therefore, the legal review timelines for each establishment will differ depending on their resources available.

6.5.1 National Heart Centre (Institut Jantung Negara)
http://www.ijn.com.my/education/clinical-research/

6.5.2 Ramsey Sime Darby Healthcare Group (previously known as Subang Jaya Medical Centre)
http://www.ramsaysimedarby.asia/eng/about-us/independent-ethics-committee

6.5.3 Nilai Medical Centre
http://www.nilaimc.com/Services-Facilities/Clinical-Trial.aspx

6.5.4 Gleneagles Penang, Loh Guan Lye Specialist Centre, Penang Adventist Hospital, Mount Miriam Cancer Hospital and Pantai Hospital
Having collaborative relationship with SMO Info-Kinetics this could be contacted for more details on the website below:
http://info-kinetics.com/clinical-solutions/smo

7 Insurance and Indemnity

7.1 Clinical Trial Insurance/Indemnity

According to the Malaysian GCP, section 5.8.1:

> "If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence."

Insurance is a system under individual or business entity or organization, where in exchange for payment (Premium) are guarantee compensation for losses resulting from certain perils under specified condition in a contract or policy.

7.2 Requirements

There are many insurance companies offering a broad range of coverage, each with its own terms and conditions. This can be confusing and a result, the process for acquiring coverage can be time-consuming. Whilst Malaysia have no legal act governing clinical trial activities (including clinical trial indemnification and insurance), the Malaysian GCP guideline states that such indemnification and insurance should be provided if required by applicable regulatory requirement(s).

It is a requirement by IEC/ MREC that all ethics submission for clinical trials must include proof of trial indemnification either by insurance certificate or letter of indemnity. These documents should indicate the protocol title and number, period of coverage and list of coverage for Malaysia sites among others. Insurance certificates that are renewed should be duly submitted to the ethics committee on an on-going basis.

Although NPCB's guidelines for application of clinical trial import licence and clinical trial exemption in Malaysia (edition 6.3) does not mention indemnity/ insurance specifically, the declaration document by Investigator (as in Appendix C of the guideline) includes a declaration by investigator stating the study has indemnity/insurance which covers for his/her activities in the clinical trial, as required in Malaysia. This declaration document must be completed and submitted by investigator from all sites for a protocol applying for CTIL/CTX.

Any institution/center or investigator involved in clinical trial should be indemnified or insured for claims arising from 1) use of investigational medicinal product (IMP), 2) procedures/activities performed for clinical trial and 3) malpractice/negligence. Many sites and investigators normally believe these are provided by sponsor/CRO.

However, in actuality, the indemnification/insurance only covers claims arising from use of investigational product and any procedures related to the particular trial. Sponsor and CRO are subject to non-indemnification for claims arising from malpractice and/or negligence by site and investigator.

Having the correct insurance coverage is part of clinical trial and the needs should be addressed as early as possible. At times, running a multi-center clinical trial in Malaysia can be complex due to different administrative or clinical practice culture and therefore, the needs of/for insurance is often misunderstood and warrants a good underwriter with expertise to cover all aspect. Whilst some centers have well documented compulsory insurance requirements outlining specific terms and conditions of the policy which must be in place, others do not.

Sponsor/CRO need to consider the product liability, geographical coverage and cost of clinical trial insurance (among others) when choosing insurance providers for a multi-center trial involving various countries. On the other hand, site and investigators must consider the coverage for all their activities related to clinical trials and also negligence when choosing insurance providers.

7.3 Coverage

The service of providing insurance by insurers (or brokers) in Malaysia is governed by the Financial Service Act 2013. Under this act, the insurers can be a Malaysia company or an international company with licence to operate in Malaysia. Some examples are Allianz, ACE, AIG, Chubb, MAA, Hong Leong, and Great Eastern.

The common clinical trial insurance policy coverage is -

1. Agreed Compensation cover – compensation to patients follows the agreed amount under the applicable clinical trial compensation clauses in the policy. It covers all the team members within the same institution or partner (which can be included with extra payment) including error or omission.
2. Legal Liability cover – it covers damages, defense and claimant's costs that are legally liable to paid.

The decision to choose a provider or a policy should be made after considering factors such as how much insurance/ limit of indemnity to provide (per claim/ per patient/ per occurrence; per aggregate/ all claim) with retention/ deductible/ out of pocket for each claim by investigator/ sponsor, and at what cost or premium. Other details that sponsor, institution or investigator should pay attention to are the contract clauses i.e. how long to cover the indemnity after the expiration of the insurance or any exclusion of pre-existing disease that will not be covered.

Another type of clinical trial insurance is "Coverage by Endorsement. Some product liability policy provides clinical trial extension coverage by an endorsement to this policy. If a particular trial is not specified and scheduled on the endorsement, it is not covered. Hence, it is important for investigator to check the policy clause for this rider or extension. This form of insurance premium is usually cheaper. Be careful when you are conducting out of label claim CT/ new indication trial, as this type of policy will be null and void.

Other liability insurance that site/investigators overlook is equipment/ material/ public liability damage coverage. This need to be purchased separately to cover the equipment loaned from sponsor i.e. spoilt by any human or natural disaster, stolen, or not returned back by patient. Another scenario is patient who fell and fractured his/her arm due to wet floor, on the day he/she comes for collecting medication only (not registered as patient or seeing investigator that day).

7.4 What information is needed?

The documents needed can vary from provider to provider and also depends on the type of coverage is being requested. As part of the insurance application process, applicant must provide an estimate of the number of subjects/ patients taking part in the clinical trial to be covered and insurers use this as basis of premium. As a general guide, the compulsory documents needed are investigator's name and annual practicing certificate (APC) from all sites involved (if applicable and for multi-site), study protocol, institute standard of care for treatment of patient with the primary indication as in the trial), patient consent form, expected approval time line from regulatory (CTIL/ CTX) and IEC (Approval letter).

For research centers, the premium can be better negotiated if the documentation as listed below can be provided. The annual premium can be competitive and much lower if centers have good track record and usually with no claims for a decade.

a. Annual revenue of the company
b. History of claim(s)
c. Rate of turnover of key personnel
d. Staff competency process
e. SOPs, accredited (ISO system), inspected by regulatory bodies (GCP, GLP etc.)
f. DSMC/DSMB – Data Safety Monitoring Committee or Board report

The policy is normally negotiated for the duration of the trial or on a yearly renewal basis. With this in mind, and it would be good to ensure a guaranteed renewable contract clause is included in the policy and the renewal is promptly made.

7.5 Claim Handling

7.5.1 Potential claims include the following:

a) A subject/patient reports on injuries that is claimed to be caused by participation in clinical trials, for which cost is not covered within the clinical trial budget and with no other means of cost coverage, especially when the claim amount is more than the access or deductible in the policy.
b) A serious side effect or any event that causes bodily injuries during clinical trial. This event will have huge financial impact, i.e. > RM20, 000
c) A technical operational staff realizes that he/she has committed some error or missed some step which would cause adverse event/effect.

7.5.2 Steps to abide when above scenario arise:

a) To inform the following personnel when such a scenario arises as soon as possible. This shall include the CEO of CRC or Institution, PI, Sponsor (depending on SOP of site)
b) The person in-charge or any other person involved should not at any point of time, admit liability or settle any claim or incur any costs or expenses in connection therewith.
c) The personnel as mentioned in 7.5.2a should immediately contact insurance agent within a time limit not exceeding three (3) days. It is advisable to use multiple forms of communications to ensure the agent is informed.

7.6 Challenges and Improvement

The gradual growth and improvement of the clinical trial landscape in the last 15 years has given a good impression to insurers who are now more willing to underwrite a Clinical Trial/ Product Liability/ Errors and Omissions policy. Previously, individual investigators had difficulty in obtaining such insurance coverage but now the process is much easier. The factors causing the change would be a well-designed protocol, use of qualified Study Coordinator (SC), engaging a CRO with an established system and processes in place and a thorough yet easily understood consent form.

Other external factors which are usually considered would be the availability of qualified investigators, medical facilities and equipment at site, patient pool for the said trial, the litigation climate (for multi-country trial), existence of a legal framework that allows a sponsor to adequately defend against a claim, and insurance requirements imposed by regulation (i.e. NPCB/ NMRR), or independent ethics committees. So far there is no fixed insured amount requested officially by

regulation or IEC. The rate is based on fair value for adequate coverage of activities in clinical trial, for example, insurance of RM100,000 for individual investigator to RM500,000 to RM 1,000 000 per occurrence for institution and RM 1,000 000 to RM 5,000 000 per clinical trial or per aggregate.

Clinical trial insurance covers for injuries regardless of fault but as the premium amount increases yearly, sponsor will exclude investigator liability coverage due to negligence. Hence, all investigator and institution/research center are advised to purchase their own professional indemnity or insurance coverage. As a measure of safeguarding the institution and the investigators involved in a clinical trial, the clinical trial agreement should have a clause stating that the sponsor will indemnify the site and the investigator against any claims arising from the use of investigational product, the procedures involved and by being involved in clinical trial provided the site and investigator have followed strictly the protocol with no errors or negligence.

The Swedish Drug Association came up with a strategy for the benefit all parties involved. They made insurance available to investigator and sites through a group facility. The facility allows investigators and sites to pool together and pay for insurance on a group basis, and this reduces the amount of premium each investigator/site pays. This means, payment of future claims will depend on the adequacy of limits available from the facility at the time of a claim. This method is worth exploring as our society is not litigious. Excessive demands by sponsor and CRO for indemnification from site or investigator due to their negligence will cause the site and investigator to shy away from taking up new trials.

The National Key Economic Area (NKEA) policy has identified clinical trials together with drug development and manufacturing as drivers of economic growth. The issue of indemnification and insurance coverage is causing site and investigator much struggle as they are forced to keep up with the increasing premium payment to ensure participant as well as staff involved in clinical trials are fully protected. In the long term, SCRPM will join with CRM in lobbying for reasonable strategy and policy involving indemnification and insurance protecting patient safety, without compromising their ability to conduct clinical trials in Malaysia.

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8 Summary Process of Clinical Trial Conduct

8.1 Industry-Sponsored Research (ISR)

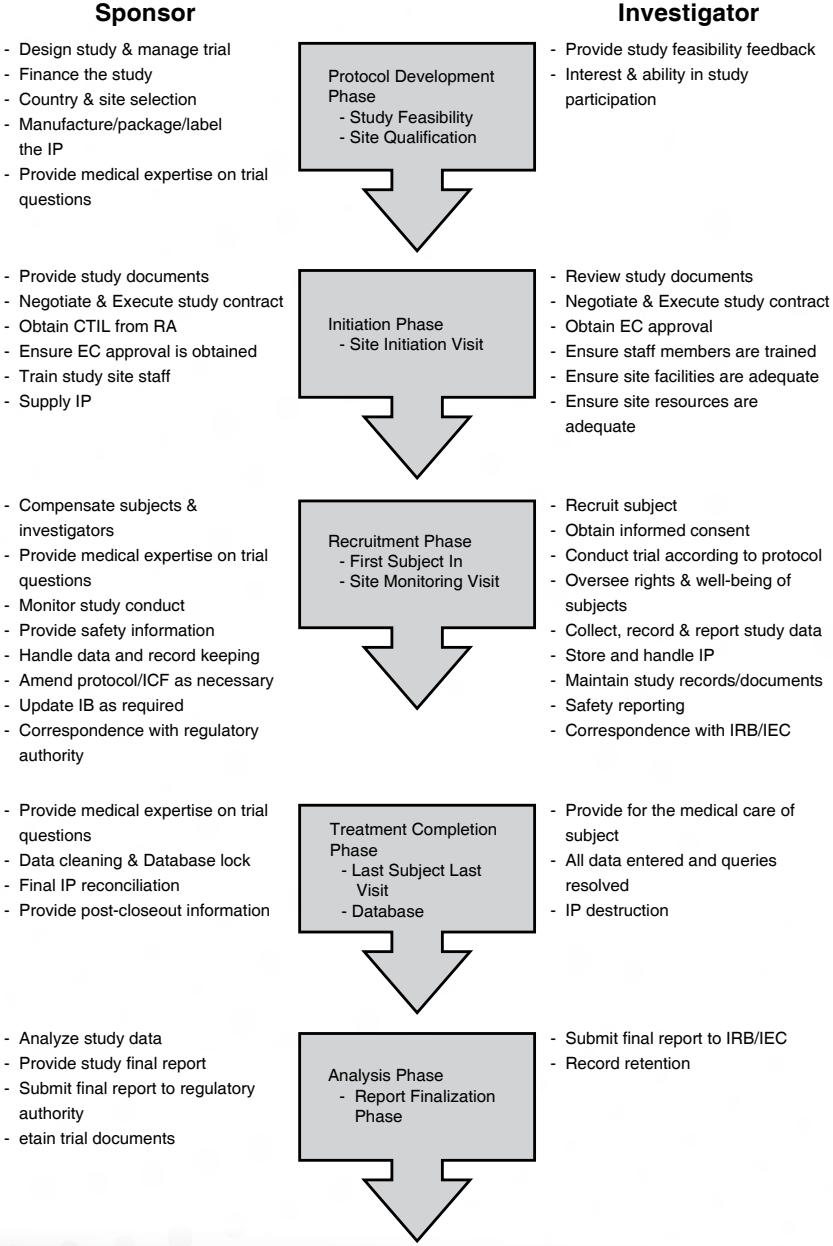
Clinical trials sponsored by companies (pharmaceutical, biotech, medical device) are called “industry sponsored trials”. According to the Malaysian Guideline for Good Clinical Practice, Sponsor means an individual, company, institution, or organization, which takes responsibility for the initiation, management, and/or financing of a clinical trial.

CRM plays an important role to improve the local ecosystem to support growth in ISR, facilitate the needs and requirements of industry players, grow the pool of capable investigators, support staff and trial sites, and improve their capabilities and capacities to conduct ISR. With the Ministry of Health’s backing and clear knowledge of the local research environment, CRM is able to provide sponsors and contract research organizations (CRO) with an extensive range of services that includes feasibility studies, investigator selection, placement and development of study coordinators, management of trial budget, review of clinical trial agreements and updates on local laws, guidelines and regulations. CRM also undertakes marketing and promotional activities to build industry awareness about the opportunities for ISR in Malaysia, and create public and patient awareness of clinical trials.

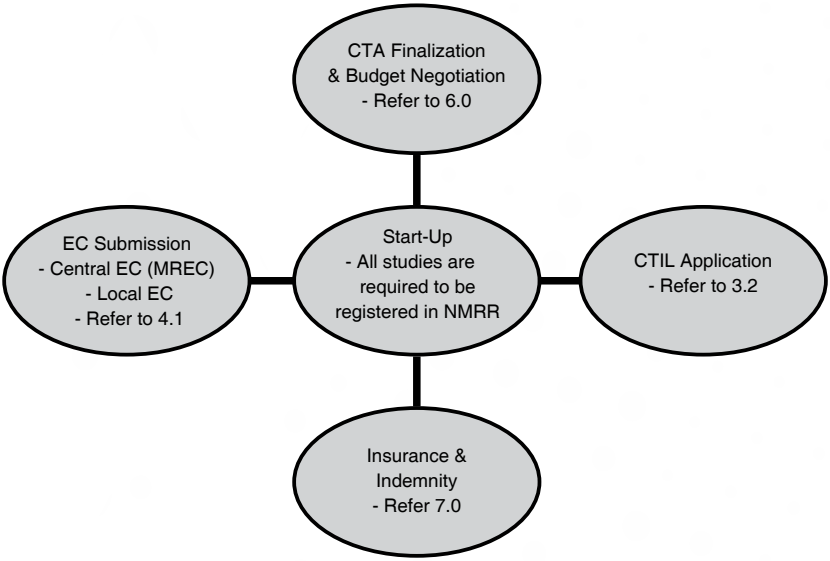
Services provided by CRM are as below:

Feasibility	• CRM or a CRO can be approached by sponsor to conduct feasibility assessment. • CRM does not charge sponsors for feasibility assessment. Duration: 5-7 working days.
Site Selection	• Sponsor to decide on the clinical trial sites based on feedback from CRM or CRO.
Start Up	• Contract Negotiation - CTA and budget review. • CRM charges RM 4000 per review of a CTA and a management fee of 15% of the value of the total trial allocation to manage the trial budget.
Study Initiation & Conduct	• CRM provides on-site fulltime SC to assist PIs. • Budget Management: CRM offers budget management services to PIs.
Archiving	• PI to outsource archiving services to archiving companies. • CRM able to assist PI.

The Summary process of conducting an industry-sponsored trial is illustrated below:



The start-up process of an ISR in Malaysia is illustrated below:



Other permits or notification that may be required for ISR conduct are:

Biological Samples Import/Export Permit	Communication Device Import Permit	Medical Device Importation Notication
• Required if the study involves exporting biological samples out of the country or importating biological samples into the country (e.g. tumor biospy, blood samples, urine samples etc). • Quantity of biological samples importation/ exportation is needed to be listed in the application submission.	• Required if the study needs to import communication devices into the country to the sutdy site (e.g. Mifi, Tablet, eDiary).	• Required if the study supplies medical device to the study site. (e.g. ECG maching, EEG machine, centrifuge, lab kits)

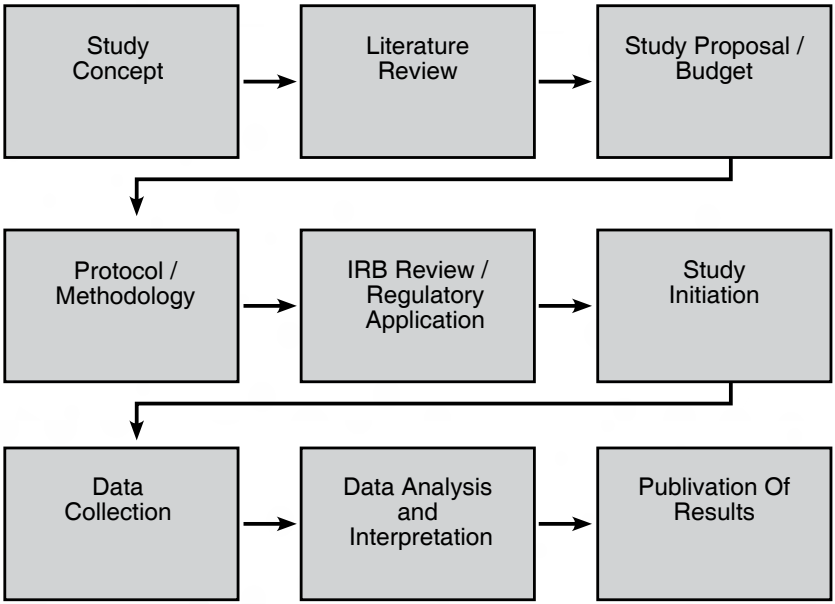
8.2 Investigator-Initiated Research (IIR)

The principal investigator can serve as the sponsor for his or her own study. An individual who both initiates and conducts, alone or with others, a clinical trial, is a sponsor-investigator. The obligations of a sponsor-investigator include both those of a sponsor and an investigator as outlined in the GCP guideline. In such cases, the research is called “Investigator-Initiated Research”.

IIR is crucial in expanding content specific knowledge that is mostly driven by local healthcare settings and patient needs. The generation of the knowledge base could potentially contribute to improve the healthcare practices and address unmet health problems. The sponsor-investigator for an IIR is responsible for the whole process of clinical research from conception of research idea to publication of results.

Network of Hospital CRC offers technical support to local investigators intending to initiate their own clinical trials. Such a program will not only assist in the smooth-running of clinical trials, but also see local investigators through all clinical trial matters, including compliance to trial regulations, trial insurance and professional indemnity, trial design and protocol development, study initiation and monitoring, pharmacovigilance, data management and training services.

The general IIR process:



Study Concept:
- Research ideas
- Problem statement

Literature Review:
- Identify available information
- Identify knowledge gap

Study Proposal and Budget:
- Project description and rationale
- Objectives
- Study Design
- Measurable variables
- Sample size
- Data collection methods
- Expected timeline
- Study budget

Protocol / Methodology:
- Similar to study proposal but a more detailed study methodology
- Title of study
- Investigator
- Summary of study
- Literature review
- Objective
- Study design
- Study site
- Study population
- Sample size calculation
- Study duration and timeline
- Informed consent
- Study treatment and/or procedures
- Data collection method
- Data storage
- Statistical analysis plan
- Ethical issues and considerations
- Privacy and confidentiality
- Conflict of interest
- Publication policy
- References

IRB Review / Regulatory Application:
- Submit study document to MREC via NMRR
- CTIL/CTX application is required if the clinical research involves the use of

unregistered IP or registered IP for unapproved indications or placebo.

Study Initiation:
- Study participant recruitment
- Informed consent taking

Data Collection:
- Data collection using case report form / questionnaire / interview
- Data entry
- Data cleaning and verification

Data Analysis and Interpretation:
- Response rate
- Demographic data
- Measurable variables (independent and dependent variables)
- Appropriate statistical analysis
- Data interpretation

Dissemination of Results:
- Written, poster and oral presentation
- Obtain DG approval

Circular by Director General of Health (DG) No. 10/2015 dated 21 Oct 2015 showed National Institute of Health (NIH) guideline on research conducted in Ministry of Health (MOH) institutions and facilities.

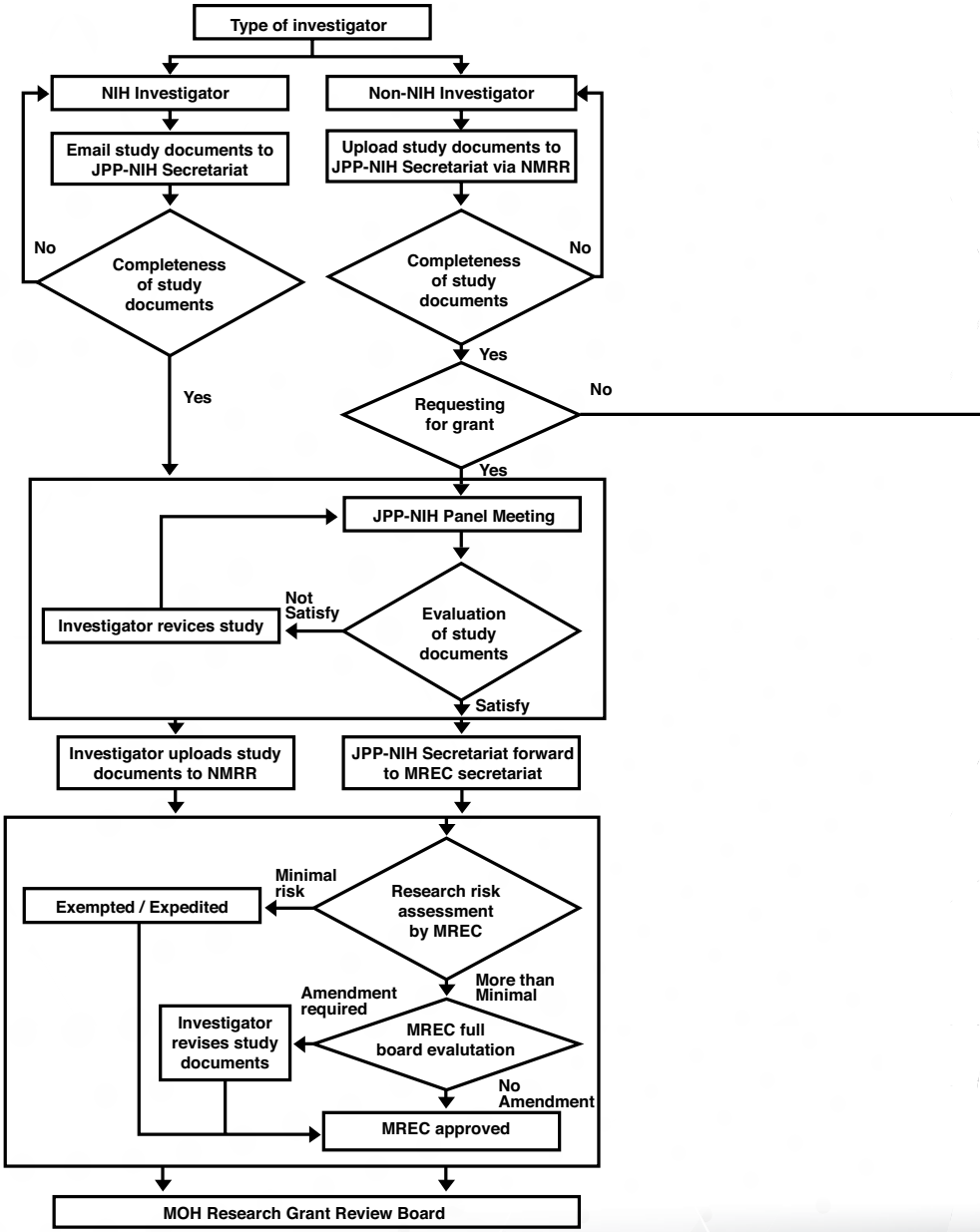
Based on the circular, all research must obtain approval from MOH by either one of the 3 pathways based on the following categories:

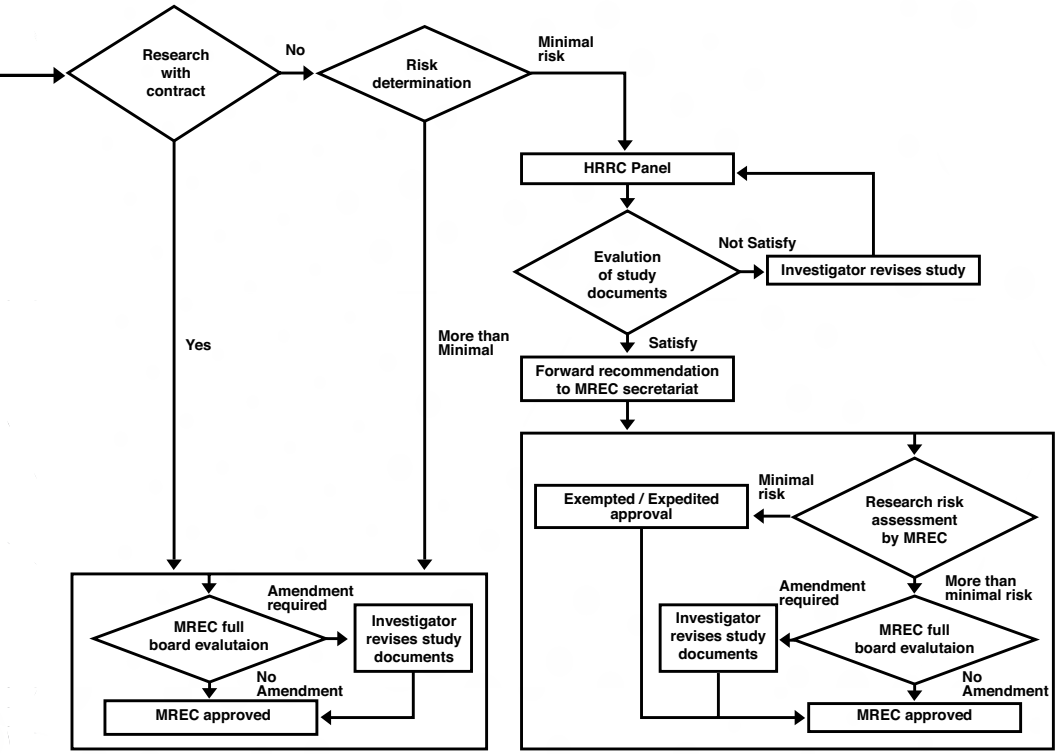
1. NIH researcher/investigator
2. Non-NIH researcher/investigator applying for grant
3. Non-NIH researcher/investigator, not requesting for grant, using MOH facilities, data and/or MOH patients.

Any form of research result dissemination must obtain prior approval from DG. Any collaborative research where external parties outside the MOH are involved, a Letter of Agreement between related MOH institution and the external parties is required.

If the IIR requires importation of investigational product to the country, an application for a Clinical Trial Import License is required.

The Summary process of grant application in MOH institutions and facilities and MREC approval process is illustrated below:




Research with contract
No
Risk determination
Minimal risk
HRRC Panel
Evalution of study documents
Not Satisfy
Investigator revises study
Satisfy
Forward recommendation to MREC secretariat
Yes
More than Minimal
Amendment required
MREC full board evalutaion
Investigator revises study documents
No Amendment
MREC approved
Exempted / Expedited approval
Minimal risk
Research risk assessment by MREC
Amendment required
More than minimal risk
Investigator revises study documents
MREC full board evalutaion
No Amendment
MREC approved

8.3 The differences of ISR and IIR

	ISR	IRR
Sponsor	Company (Pharmaceutical, Biotech, Medical Device)	Investigator
Funding	Company	Research grant or self-funding
Study design	Study clinician from the sponsor company	Investigator
Primary Objective	Commercial value	Local context specific knowledge/evidence
Study Management	Sponsor study team	Investigator study team
Intellectual Property	Sponsor will own any patentable inventions developed	Investigator will own any patentable inventions developed

8.4 Compassionate Use Program

The compassionate use program in Malaysia is available as an extension to an approved clinical trial protocol. Through this program, only subjects who had previously enrolled in the approved clinical trial are allowed to continue the use of the unregistered medicinal product with the approval of the DCA. In such case, CTIL applicant shall apply for additional quantity for compassionate use in order to import the product via CTIL. The additional quantity for compassionate use program will only be approved for 6 month. If there is a need to continue the compassionate program for more than 6 months the applicant is required to reapply for an additional quantity of IP.

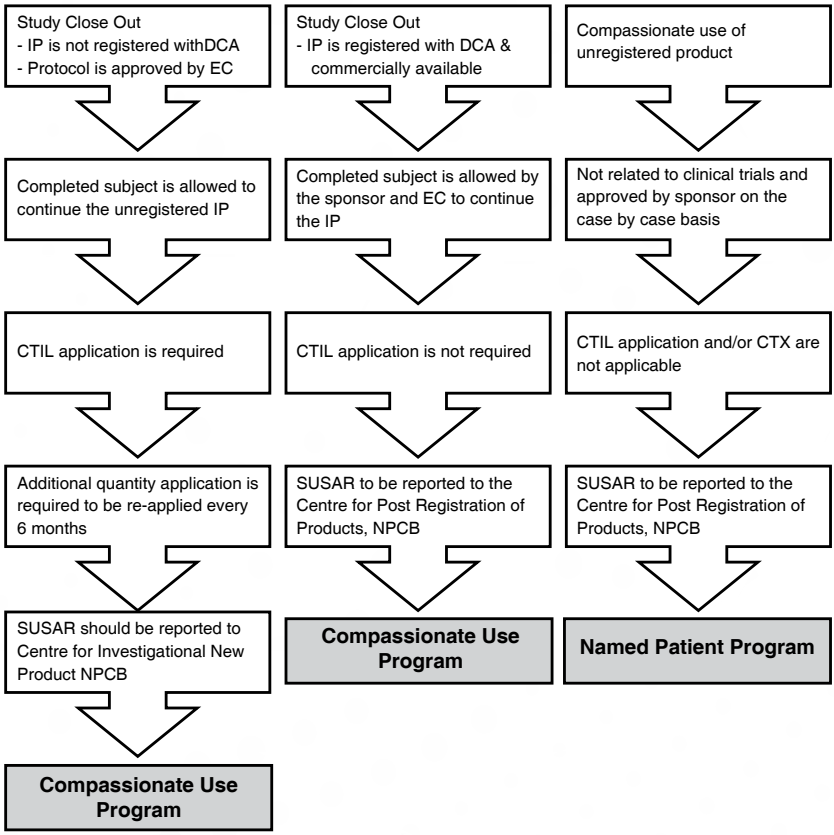
As the compassionate use program is an extension of a completed clinical trial and subjects will be provided with continued treatment with the unregistered product, all serious, unexpected adverse drug reactions should be reported to the Centre for Investigational New Product.

In the event that the product to be used by the subjects of the completed clinical trial is registered with the DCA and commercially available, all suspected local adverse reactions should be reported to the

Pharmacovigilance/ADR/Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) Unit, Centre for Post Registration of Products in accordance with their established procedures.

Meanwhile, for named patient programs involving compassionate use of unregistered product that require approval by Director General of Health, does not fall under The Malaysian Guideline for Application of Clinical Trial Import License and Clinical Trial Exemption, Therefore, any arising SUSAR should be reported to the Pharmacovigilance / ADR / MADRAC Unit, Centre for Post Registration of Products in accordance with their established procedures.

Overview of conditions for compassionate and named patient program:



8.5 Non-Interventional Study (NIS)

'Non-interventional study': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. NIS includes Post-Marketing Surveillance studies (PMS), Post Authorization Safety Studies (PASS), cohort studies and case-control studies.

NIS may be either an ISR or IIR. The process flow of NIS is similar to ISR except that the application of Clinical Trial Import License is not required. Notification of study to NPCB is also not required as the study does not involve administration of medicinal product.

9 Key Contacts for Clinical Trial Conduct

9.1 Regulatory Bodies

Name	CR Related Activity	Website Link
National Pharmaceutical Control Bureau (NPCB)	Clinical Trial Import License Application	http://portal.bpfk.gov.my/
Medical Device Authority (MDA)	Notification of Medical Device Importation for Clinical Trial	http://www.mdb.gov.my/mdb/
Division of Disease Control Ministry of Health	Biological Import/ Export Permit Application	Application process through BLESS: https://open.bless.gov.my/bless/
SIRIM QAS International Sdn. Bhd.	Emitting Device Import Permit Application	http://www.sirim.my/

9.2 Independent Ethics Committee (IEC)

All IEC that approved drug related trial MUST be registered with DCA. The list of registered IEC may be obtained from NPCB website: http://bpfk.moh.gov.my/images/Guidelines_Central/Guidelines_on_Clinical_Trial/Senarai_Jawatankuasa_Etika_yang_berdaftar_dengan_PBKD.pdf

Name	Website Link
Medical Research Ethics Committee (MREC)	http://nih.gov.my/web/mrec/ Application process through NMRR: https://www.nmrr.gov.my/fwbLoginPage.jsp
Joint Penang Independent Ethics Committee (JPEC)	http://info-kinetics.com/jpec
Medical Ethics Committee, University Malaya Medical Centre (MEC,UMMC)	https://eservices.ummc.edu.my/iresearch/login.asp

Name	Website Link
Independent Ethics Committee Sime Darby Healthcare (IECSDH)	http://www.ramsaysimedarby.asia/eng/about-us/independent-ethics-committee
Sunway Medical Centre Independent Research Ethics Committee (SREC)	http://sunwaymedical.com/about-clinical-research-centre/12255-2/
International Medical University (IMU) Joint Committee of the Research and Ethics Committee (IMUJC)	http://irdi.imu.edu.my/policies-and-guidelines
Jawatankuasa Etika Penyelidikan Institut Jantung Negara (IJN)	http://www.ijn.com.my/education/clinical-research/
IIUM Research Ethics Committee (IREC)	http://iiumedic.net/irec/v1/
Joint Ethics Committee School Of Pharmaceutical Sciences, Universiti Sains Malaysia (USM) – Hospital Lam Wah Ee On Clinical Studies	Not Available
Jawatankuasa Etika Penyelidikan, Universiti Teknologi MARA (UiTM)	http://uitmethics.uitm.edu.my/v1/index.php
Jawatankuasa Etika Universiti Untuk Penyelidikan Melibatkan Manusia, Universiti Putra Malaysia (JKEUPM)	http://www.rmc.upm.edu.my/jkeupmbm
Jawatankuasa Etika Penyelidikan (Manusia), USM (JEPeM)	http://www.jepem.kk.usm.my/
Jawatankuasa Etika Penyelidikan, Universiti Kebangsaan Malaysia (JEPUKM)	http://www.ppukm.ukm.my/sppi/muat-turun-borang-penyelidikan/

9.3 Government Support Bodies

Name	Function	Website Link
National Committee for Clinical Research (NCCR)	Steering committee for Clinical Research in Malaysia	http://www.nccr.gov.my/
Clinical Research Centre (CRC)	Promote, support and conduct investigator initiated research (IIR) by healthcare providers at MOH	http://www.crc.gov.my/
Clinical Research Malaysia (CRM)	To establish Malaysia as a preferred destination for Industry Sponsored Research (ISR	http://www.clinicalresearch.my/

9.4 Society

Name	Function	Website Link
Society of Clinical Research Professionals Malaysia (SCRPM)	Promote Clinical Research in Malaysia through education and networking	http://scrpm.ucoz.com/

9.5 Local CRO

Name	Website Link
Info-Kinetics	http://info-kinetics.com/
Klinsel	http://klinsel.com.my/v2/
Questra Clinical Research Sdn. Bhd.	http://www.questra.com.my/
Veras Research Sdn. Bhd.	http://www.verasresearch.com/
MyXMO	http://myxmo.com.my/

9.6 International CRO That Are Based In Malaysia

- Quintiles Sdn. Bhd.
- PAREXEL International (Malaysia) Sdn. Bhd.
- Covance Services Malaysia Sdn. Bhd.
- INC Research
- inVentiv Health (Malaysia) Sdn. Bhd.
- Pharmaceutical Product Development (M) Sdn. Bhd. (PPDI)
- Novotech Clinical Research (M) Sdn. Bhd.
- InClinica
- D2 Bio Solutions Sdn. Bhd.
- Veeda Clinical Research SE Asia
- George Clinical

List above is not exhaustive, for a list of CROs present in Malaysia, please refer to CRM website (http://www.clinicalresearch.my/sponsors-cros/).

9.7 Pharmaceutical Company

Refer to Pharmaceutical Association of Malaysia (PhAMA) membership directory: http://www.phama.org.my/index.cfm?&menuid=15

If you have any enquiries regarding the key contacts for clinical trial conduct in Malaysia, you may refer to SCRPM or write to us at scrpmalaysia@gmail.com

10 Glossary

10.1 Adverse Drug Reaction (ADR)

In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

10.2 Approved Training in Good Clinical Practice

Training which is approved by the National Committee for Clinical Research (NCCR). The content of the training must incorporate the curriculum as stipulated by the committee.

10.3 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor’s Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

10.4 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

10.5 Clinical Trial Exemption (CTX)

An approval by the DCA authorizing the applicant to manufacture any local product for the purpose of clinical trial.

10.6 Clinical Trial Import Licence (CTIL)

A license in Form 4 in the schedule of The Control of Drugs and Cosmetics Regulations of 1984, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product.

10.7 Contract

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

10.8 Contract Research Organization (CRO)

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

10.9 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

10.10 Drug Control Authority (DCA)

A regulatory authority established for the purpose of regulating the Control of Drugs and Cosmetics Regulations, 1984.

10.11 Good Clinical Practice (GCP)

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

10.12 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

10.13 Independent Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

10.14 Informed Consent

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

10.15 Inspection

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

10.16 Investigational Product

A pharmaceutical form of an active ingredient including plant/ animal-derived medicinal products or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization 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.

10.17 Investigator

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

10.18 Investigator's Brochure (IB)

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

10.19 National Committee for Clinical Research (NCCR)

A committee established for the purpose of coordinating and promoting clinical research in Malaysia, chaired by the Director General of Health, Ministry of Health Malaysia.

10.20 National Institutes of Health (NIH)

National Institutes of Health (NIH) is a network of Ministry of Health (MOH) research institutes. NIH was approved in the 7th Malaysian Plan (7MP), and officially launched by Hon. Minister of Health Malaysia on 11 August 2003. NIH is consisting of 6 institutes which are:

- Institute for Medical Research (IMR)
- Institute of Public Health (IPH)
- Clinical Research Centre (CRC)
- Institute for Health System Research (IHSR)
- Institute for Health Management (IHM)
- Institute for Health Behavioural Research (IHBR)

NIH aims to create seamless continuum from identification of research priorities, conduct of research to utilization of research findings.

The National Institutes of Health is under the preview and headed by the Deputy Director General of Research & Technical Support [DDG(R&TS)].

10.21 National Medical Research Register (NMRR)

NMRR is a web-based service initiated by the National Institutes of Health (NIH) of the Ministry of Health (MOH). It is a web based tool designed to support the implementation of the National Institute of Health (NIH) guideline on the conduct of research in the Ministry of Health Malaysia (MOH).

Current MOH policy on research, as specified in the guideline, requires:

- Registration of all research that involves MOH personnel OR that is to be conducted in MOH facility OR to be funded by MOH research grant
- Review & approval of the research by a designated entity to whom authority has been delegated for the purpose
- In addition, research involving human subjects requires prior review and approval by the MOH Research and Ethics Committee (MREC)
- Approval of all research publications, whether in the form of research report, journal article or conference proceeding, by the NIH initially and thereafter by the Director General of MOH

The NMRR is thus specifically designed to enable:

1. Online registration of research. This brings us in line with international practice which requires medical research, especially clinical trial, to be registered in publicly accessible research registers. This is to ensure transparency and to increase public trust in the conduct of medical research; as well as to inform physicians and prospective volunteers about ongoing research in which they may wish to enroll.

2. Online submission to an appropriate authority for approval, as well as online review of the submitted research by relevant appointed reviewers. The online system ought to reduce the research review time as well as to enable investigators to track the status of their research online.

3. Online submission of research publication to the NIH for approval.

4. Finally, the NMRR also enable MOH management to document the level of research activity in the MOH, and also to track the progress of the research it has approved and/or provided support such as funding.

10.22 Poison

Any substance specified by name in the first column of the Poisons List and includes any preparation, solution, compound, mixture or natural substance containing such substance, other than an exempted preparation or an article or preparation included for the time being in the Second Schedule.

10.23 Protocol

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

10.24 Regulatory Authority

Bodies having the power to regulate. In the Malaysian Guideline for Good Clinical Practice the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

10.25 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

10.26 Sponsor

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

11 Acronyms

ADR	Adverse Drug Reactions
AE	Adverse Event
APC	Annual Practising Certificate
ARC	Annual Retention Certificate
BE	Bioequivalence
CIEP	Committee for Inspection and Evaluation of Premises
CINP	Centre for Investigational New Product
CIOMS	Council for International Organizations of Medical Sciences
CMA	Compliance Monitoring Authorities
CRC	Clinical Research Centre
CRM	Clinical Research Malaysia
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CTIL	Clinical Trial Import Licence
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
DG	Director General
DSMC/DSMB	Data Safety Monitoring Committee or Board
EC	Ethics Committee
EPP	Entry Point Project
ETP	Economic Transformation Programme
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GGE	General Government Expenditure
GGHE	General Government Health Expenditure
GLP	Good Laboratory Practice

GMP	Good Manufacturing Practice
GNI	Gross National Income
GST	Goods and Services Tax
ICF	Informed Consent Form
ICH-GCP	International Council on Harmonisation - Good Clinical Practice
IEC	Independent Ethics Committee
IIR	Investigator-Initiated Research
IA-HOD-IA	Investigator Agreement, Head of Department and Institutional Approval
IRB	Institutional Review Board
ISR	Industry-Sponsored Research
JEPeM	Jawatankuasa Etika Penyelidikan (Manusia), University Sains Malaysia (Human Research Ethics Committee, Universiti Sains Malaysia)
JPEC	Joint Penang Independent Ethics Committee
MAD	Mutual Acceptance of Data
MADRAC	Malaysian Adverse Drug Reactions Advisory Committee
MCMC	Malaysian Communications and Multimedia Commission
MDA	Medical Device Authority
MOH	Ministry of Health
MOPI	Malaysian Organisation of Pharmaceutical Industries
MPS	Malaysian Pharmaceutical Society
MREC	Medical Research and Ethics Committee
NCCR	National Committee for Clinical Research
NIH	National Institutes of Health
NKEA	National Key Economic Area
NPCB	National Pharmaceutical Control Bureau
OECD	Organization of Economic Cooperation and Development
PASS	Post Authorization Safety Studies
PD	Protocol Deviation
PDPA	Personal Data Protection Act
PhAMA	Pharmaceutical Association of Malaysia

PI	Principal Investigator
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PIS	Patient Information Sheet
PMS	Post-Marketing Surveillance Studies
REC	Research Ethics Committee
RECUKM	Research Ethics Committee, Universiti Kebangsaan Malaysia
SAE	Serious Adverse Event
SC	Study Coordinator
SCRPM	Society of Clinical Research Professionals Malaysia
SOP	Standard Operating Procedure
SREC	Sunway Medical Centre Independent Research Ethics Committee
SSO	Single Sign On
SUSAR	Suspected Unexpected Serious Adverse Reaction
THE	Total Health Expenditure
TVF	Trial Validation Form
UiTM	Universiti Teknologi Mara
UKMMC	Universiti Kebangsaan Malaysia Medical Centre
UMMC	University of Malaya Medical Centre
USM	Universiti Sains Malaysia
VAT	Value Added Tax
WHO	World Health Organization

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