CRM
CLINICAL RESEARCH MALAYSIA
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PHASE 1 REALISATION PROJECT REPORT (P1RP)

(2016 - 2021)

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INTRODUCTION

Clinical research is essential to the path of new medicine development and is conducted to produce safe and effective treatment. It is a highly regulated sector, with much attention focused on the safety of trial participants, hence spelling the importance of finding the right sites and investigators for clinical research. Since early 1990s, Malaysia has been conducting clinical research, many of which are sponsored research by the global pharmaceuticals and medical device companies. Malaysia's uniqueness in ethnic diversity is an added feature when comes to understanding the effectiveness of new medicine in Asian population. In addition, with the burden of non-communicable diseases, the country already has the experienced medical professionals, established medical infrastructures and a strong regulatory framework in place.

Recognising the value to drive especially the sponsored clinical research industry, Clinical Research Malaysia was established as a corporatized MOH company in 2012. The organization succeeded in achieving all its formation goals in 2020, making it the first MOH owned company to accomplish its targets. By end of 2021, over 1800 sponsored research were conducted in Malaysia since 2012, generating a cumulative Gross National Income of RM 834 million, with over 2000 skilled jobs creation in clinical research.

Reviewing back the data on sponsored clinical research conducted, close to half of the studies are of Phase 3 studies, with an obvious gap noted in the conduct of early phase studies in Malaysia, namely First-in-Human Studies and Phase 1b studies. As most clinical trials rely on the conventional drug development design, it is especially important for Malaysia to be in the footprintof biopharmaceutical and biotechnology industries of early phase studies as this would result in a spillover effect of more Phase 2 and Phase 3 trials. For patients, it increases the opportunity to receive novel medications or treatment that is yet available in the market. For the nation, there is a huge knowledge transfer opportunity as early phase trials also spurs the increase in skills and experience of study teams that would enable the ecosystem for locally developed treatments/ therapeutics.

The Government of Malaysia recognises the potential of positive impact of early phase trials for patients, as well as the value of scientific advancement and economic growth early phase studies brings. Hence, there is paradigm shift to also focus efforts in further progressing Malaysia's clinical trial capabilities by setting-up new initiatives to drive early phase clinical research capacity and capabilities.

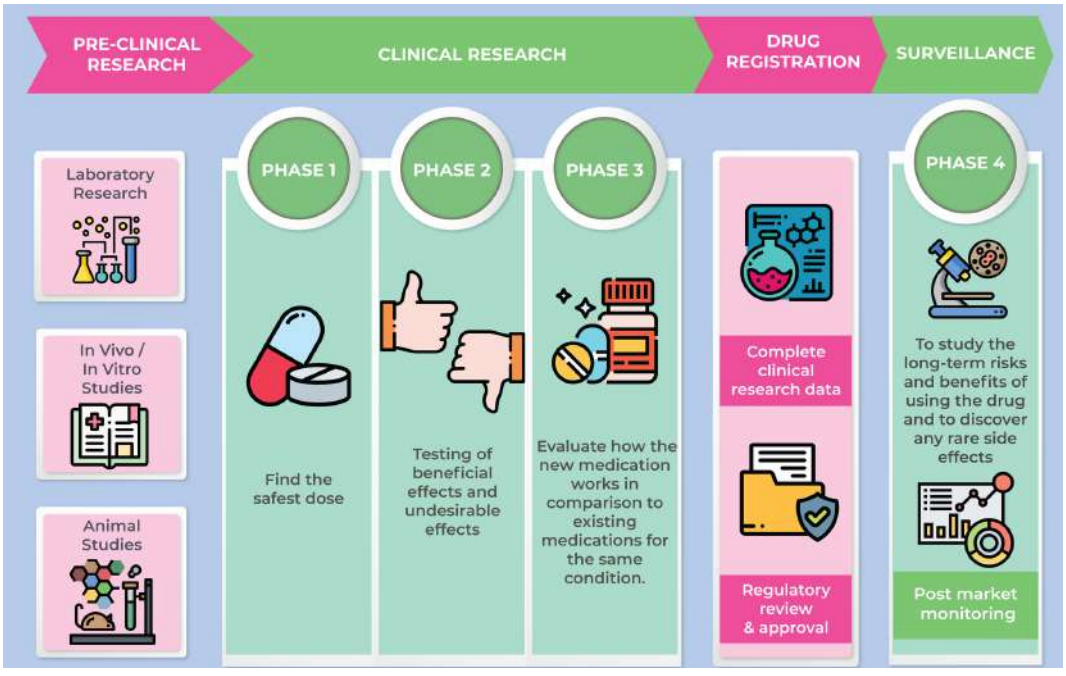
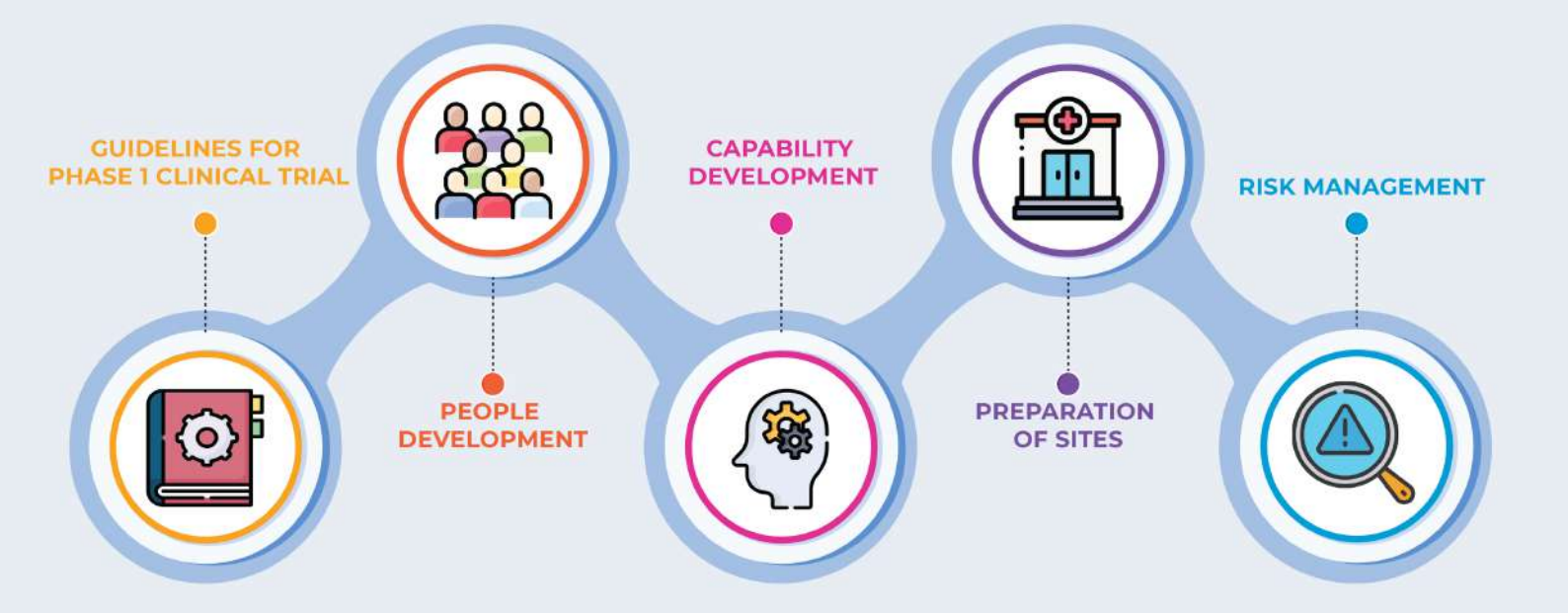


Illustration on Conventional Drug Development Phases

ABOUT PHASE 1 REALISATION PROJECT

CRM developed the Phase 1 Realisation Project (P1RP) with the support of the Ministry of Health, to ensure Malaysia's readiness for safe and quality conduct of early phase trials, especially First-in-Human trials. Following several discussions and consult by local and international key opinion leaders, five pillars were identified to be developed under the P1RP blueprint, which are the establishment of guidelines for conducting Phase 1 clinical trials in the country, people development, capability development, preparation of sites and risk management.



The Five Pillars under the Phase 1 Realisation Project

The project was initiated on 20 May 2016, by then Minister of Health Malaysia, YB Datuk Seri Dr Subramaniam. The strategy approached is multi-pronged, focused on ensuring regulatory agencies are equipped with the right knowledge to review Phase 1 clinical trials as well as conforming to international standards, training local experts to analyse early phase trials through engagement with international consultants, preparation of clinical trial unit at hospitals to conduct Phase 1 studies, and the development on an action plan to manage and mitigate any given crisis that may occur during the conduct of clinical trial.

The project is developed as a five-year plan, with the Government of Malaysia investing a RM2.6 million budget for CRM to drive these initiatives under the pillars.

Photo taken during launch of P1RP by the Minister of Health Malaysia, dated 20 May 2016

GUIDELINES FOR PHASE 1 CLINICAL TRIALS

There was no guideline specific to early phase trials in Malaysia prior to the roll-out of the P1RP. This had become the first focus under the P1RP, as the lack of guiding document is often a deterrent to many international stakeholders, especially in understanding the needed regulatory requirements of the country.

To initiate the setup, a series of workshops were held in 2016, an effort which saw the gathering of experts and investigators from Ministry of Health, Ministry of Higher Education, ethics committees, regulatory bodies and even industry experts. International key opinion leaders were also invited to provide their input in these workshops as subject matter experts. The Association of the British Pharmaceutical Industries (ABPI) 2012 document was the main reference document in developing the early phase guidelines, as the former document had already expanded its content, adapting to the latest changes in conducting FIH trials.

The MP1CTG Workshops, dated 20 August 2016 & 19 November 2016 respectively

Following this, The Malaysian Phase 1 Clinical Trial Guidelines (MP1CTG) was launched by Dato' Dr Goh Pik Pin, the former Director of Institute for Clinical Research on 2 November 2017. The guideline included existing procedures of local authority bodies and agencies and have adapted the relevant areas to facilitate the applicability of ABPI guidelines in Malaysia.

The launch of Malaysian Phase 1 Clinical Trial Guidelines, dated 2 November 2017

The MP1CTG became the first ever Phase 1 guidelines produced in Malaysia and was the precursor document to the Malaysian Guideline for Phase I Unit Inspection & Accreditation Programme developed by the National Pharmaceutical Regulatory Agency (NPRA) in 2018. The guideline was also adapted within the existing NPRA guideline for Clinical Trial Import License (CTIL)/ Clinical Trial Exemption (CTX). With several referring guidelines in place, Malaysia's readiness to conduct early phase studies is made visible to interested parties.

Malaysian Phase 1 Clinical Trial Guidelines & Malaysia Guideline for Phase 1 Unit Inspection & Accreditation Program

PREPARATION OF SITES

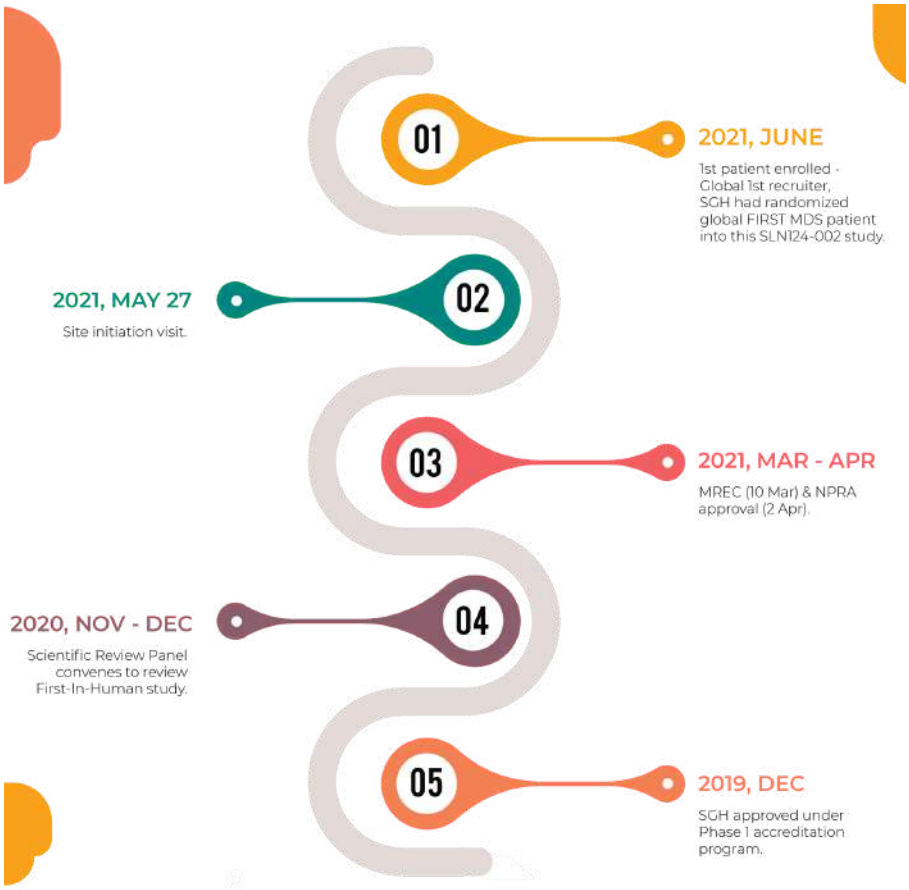
Following the published 2018 Guideline for Phase I Unit Inspection & Accreditation Programme, study sites are required to be accredited under NPRA's programme prior to conducting FIH study. Following this, in December 2019, Sarawak General Hospital (SGH) became the first facility in Malaysia to be provisionally accredited under Phase 1 Unit Accreditation Program by NPRA.

Prior to receiving its accreditation, the site went through several preparation supported by CRM, including facility/ infrastructure upgrades as well as laboratory certifications (ISO 17025:2017 and ISO 15189: 2014), to perform the required drug plasma concentration analysis and for medical testing. In addition to its already existing research facility, the Phase 1 unit in SGH is also equipped with:

- Dedicated 10 HDU bedded ward with 2 ICU equipped beds
- Temperature monitored drug storage areas with restricted access
- Sample-handling area with refrigerated centrifuge
- Refrigerators and freezers (all temperature monitored) for drug and sample storage
- Synchronized digital clock
- Physiology laboratory with instruments for cardiac, lung respiratory and neurological system assessment
- Dedicated procedure room
- Subject recreation area
- Wi-Fi enabled facility with remote access monitoring capability

Facilities in SGH Phase 1 Unit

In 2021, the first FIH study was initiated at SGH, led by Dr Chew Lee Ping, a consultant haematologist. The study, which was on patients with thalassemia/ myelodysplastic syndrome, performed exceedingly well, with Dr Chew being recognised as the first global recruiter for the study.



Timeline of SGH FIH Study Achievement

With the success of SGH as a Phase 1 facility, more facilities are slated to be recognised under the NPRA Phase 1 program. As of January 2022, Ampang Hospital has been inspected by NPRA, aiming to become the second accredited FIH site in the country.

PEOPLE DEVELOPMENT

Under the P1RP strategy of people development, the focus was to develop the capabilities of regulators and investigators to ensure safe and quality conduct of early phase trials, that is also sufficiently evaluated and monitored by the regulatory agency, in accordance with the international standards and local requirements.

Following this, in 2017, CRM sponsored two NPRA officers (Ms Tang Sia Chin and Ms Nur Atiqa Kamal Rodin from Evaluation and Safety of Investigational New Product Section), for their postgraduate studies (Masters in Experimental Cancer Medicine) at Manchester University, UK. During the program, both officers had an attachment at The Christie, where they were trained on the specifics for designing and delivering Phase 1 studies, in addition to evaluating pre-clinical data provided prior to the initiation of a clinical trial program. CRM also sponsored Ms Lee Wei Xin from the same NPRA section in 2018, for her pursuit of Master of Science program in Clinical Pharmacology at King's College, London.

The signing of the Education Scholarship Agreement between CRM and NPRA officer, Ms. Lee Wei Xin, dated 7 September 2018

With the return of all three officers to NPRA, the regulatory's capability in FIH dossier evaluation is further enhanced. To further support the regulatory review structure for FIH studies, an external Panel of Expert (POE) was also established within NPRA, made up of expert scientific members independent of NPRA. The POE functions as to conduct parallel review of the regulatory dossier, which would later be evaluated during the technical meeting. With the parallel pathway within NPRA set-up to ensure quality regulatory review of FIH studies, NPRA proceeded in evaluating and approving the first FIH study in March 2021 that later was conducted in Sarawak General Hospital.

There was also a need to further develop the capabilities of Malaysian investigators in the conduct of FIH studies. Ensuing this, initiatives for investigator attachments in reputable phase 1 centres were explored. In 2020, Dr Voon Pei Jye, a Medical Oncologist from Sarawak General Hospital was accepted for a Clinical Fellowship training program at Princess Margaret Cancer Centre (PMCC) which is affiliated with the University of Toronto, Canada. Dr Voon was one of six candidates around the world that was accepted into the reputable program in PMCC, which is among the top 5 and largest cancer research centres in the world. During his one-year fellowship, Dr Voon participated in multiple research projects, and taking up clinical and teaching duties specific to the Phase 1 program. Following his return to SGH in 2021, Dr Voon is actively pursuing Phase 1 feasibility requests as well as developing SGH's team capability in FIH trials.

Dr Voon Pei Jye (R) and Dr Albiruni Razak (L), a Malaysian oncologist based in PMCC, with leading work in sarcoma research

CAPABILITY DEVELOPMENT

As part of the capability development pillar of P1RP, the Scientific Review Panel (SRP) for Phase 1 Studies was established to support the Medical Research and Ethics Committee (MREC) in performing scientific evaluations of FIH trials undertaken by and/or conducted in clinical trial sites in Malaysia. The scope of review includes all FIH studies on new chemical, biological and biosimilar drugs not registered in Malaysia.

The SRP is established under the purview of the National Committee for Clinical Research (NCCR), and its members appointed by the Minister of Health Malaysia. The selection and appointment of SRP members are based on their relevant scientific expertise in areas such as clinical sciences, pharmacology/ clinical pharmacology, toxicology and biostatistics.
THE SRP was formally established in 2018, with 11 members in the panel, from various research institutions and organisations in Malaysia, United Kingdom, Hong Kong, Macau & Germany. CRM functions as the secretariat for the panel. The standard operating procedure was also established, to ensure the review of FIH study is structured (including a published annual calendar on SRP review meeting dates), with timeliness and quality of review prioritised.

In November 2020, the SRP committee convened for its first review meeting to evaluate a FIH study led by Dr Chew Lee Ping in SGH. The scientific recommendation was provided to MREC in December 2020, and factoring these evaluations, MREC provided the ethics approval for this study in March 2021.

1st row (L to R): Prof Dr Abdul Rashid (Chairman) (An Nur Specialist Centre, Malaysia), Dr Linda Hakes (Independent Consultant, Germany), Prof Dr Chim Lang (University of Dundee, Scotland), Prof Brian Tomlinson (The Chinese University of Hong Kong, Prof David Kerins (University College Cork, Ireland) & Prof Bernard MY Cheung (The University of Hong Kong)

2nd row (L to R): Prof Datin Dr Zahurin Mohamed (University of Malaya, Malaysia), Prof Dr Loke Yoon Kong (University of East Anglia, UK), Dr Jacob George (University of Dundee, Scotland), Dr Joseph Cheriyan (Cambridge University Hospital, UK) & Dr Ami Fazlin Syed Mohamed (Institute for Medical Research, Malaysia)

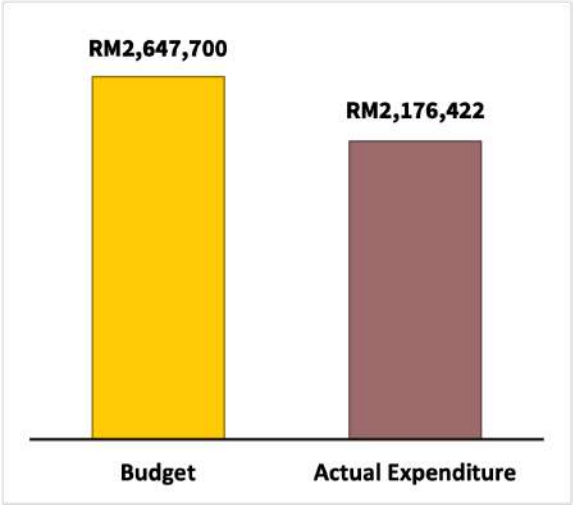
RISK MANAGEMENT

Part of the P1RP initiative was also on the preparation and training of risk management guidelines, and to manage any crisis in relation to the conduct of early phase clinical trials. Ensuing this, a crisis management training was conducted in 2016, which was followed with the development of CRM's Crisis Manual in 2017. The manual was developed to ensure all actions are coordinated, timely, accurate, consistent and effective in minimising the potential for confusion, rumour and misinformation. The Crisis Manual also includes standard operating procedures to prepare and manage all types of crises requiring immediate attention and action during early phase trials (i.e. unexpected side effect from a clinical trial).

Crisis Management Training, dated 24 October 2016

RESULTS

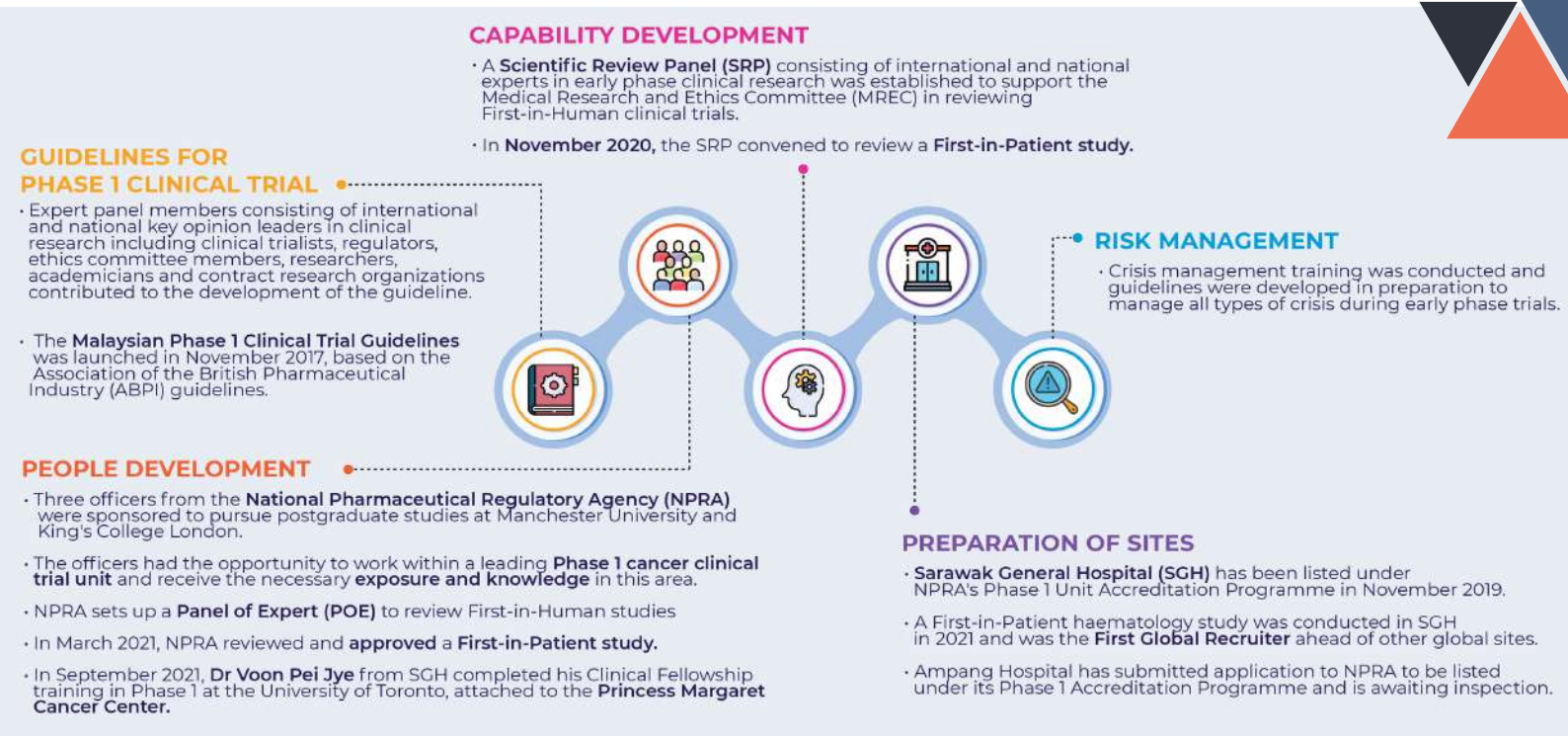
With the return of Dr Voon Pei Jye from PMCC, following his early phase fellowship program, CRM has successfully wrapped-up its P1RP initiatives within 5 years from inception.



P1RP Budget versus Actual Expenditure

Distribution of Actual Expenditure between 5 pillars of P1RP

From the budgeted RM 2.6 million, CRM has executed the 5 pillars within the budget, with 18% savings (total expense of RM 2.2 million).



With the completion of this project, CRM has further supported the enhancement of FIH capabilities and capacities in Malaysia, by delivering on the needed framework, trained regulators, equipped study site and experienced study team in place.

WHAT'S NEXT

Since 2020, CRM has completed multiple feasibility studies on FIH trials, especially on Covid-19 therapies & immuno-oncology studies. This, which had culminated to the successful awarding of the ongoing First-in-Patient study at Sarawak General Hospital and has paved the way for increased early phase trials in the country, i.e Phase 1b and Phase 2 studies. CRM will continue to participate in more promotional activities, especially in international meetings and leveraging itsexisting network, to increase Malaysia's visibility as a valuable trial destination for early phase studies.

The readiness of the country in early phase studies also includes the support and coordination of all the clinical research stakeholders in Malaysia. Recognising the need for safety of health subjects in clinical trials, the Institute for Clinical Research (ICR) has developed the National Healthy Volunteer Research Registry (NHRVR), which was launched in 2021, with the aim to prevent over-volunteering into clinical trials among healthy volunteers. This has also been adapted into NPRA's requirement, in which all clinical trials involving health volunteers (many of which FIH and bioequivalence studies) will be required to adapt the NHRVR platform, effective June 2022. With the implementation of this measure, the emphasis on safety of healthy volunteers in clinical trials is further pronounced.

Lastly, from the regulatory point of view, the regulation of FIH studies framework has evolved with the gaining of knowledge and expertise. From prior requirement of only reviewing FIH investigational product of New Chemical Entity (NCE) and herbal products, NPRA has now expanded its scope to also accepting CTX applications involving locally developed Covid-19 vaccines (biologics). This is in line with the country's National Vaccine Development Roadmap which aims for Malaysia to develop its capabilities in vaccine development and production. At present, NPRA is also evaluating its preparedness for review and monitoring of studies involving other biologics such as immunotherapies as well as cell and gene therapies.

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D-26-06. Menara Suezcap 1, KL Gateway, No. 2 Jalan Kerinchi
Gerbang Kerinchi Lestari, 59200 Kuala Lumpur, Malaysia
T: +603-7931 5566 | F: +603-7931 9940 | E: contact@clinicalresearch.my