By Clinical Research Malaysia

CRM bulletin

of Clinical Research and Therapy

ISSUE 11

A Step Forward in Clinical Research

KNOWING CLINICAL TRIALS 101

MREC: ISR Performance Statistics

SPECIAL COVERAGE

Malaysia's Clinical Research Ecosystem

FEATURED SITE

CRC Hospital Umum Sarawak

RESEARCH PERSONALITY

Dr. Voon Pei Jye

ABOUT CLINICAL RESEARCH MALAYSIA

Clinical Research Malaysia (CRM) exists to advance global health solutions for a brighter, more hopeful future for the people by providing speedy and reliable end-to-end clinical research support for quality studies. As these studies unfold, we work together with our partners to create an impetus in delivering better treatment to our end consumers, while at the same time creating high-skilled job opportunities.

The strength of our operation lies in our innate understanding of the local clinical research landscape and implementation of international standards. This, when considered in parallel to the fundamental backing of the government ministries, provides us with an incomparable advantage, as we work hand-in-hand with our partners from the nascent stages of development to materialisation of the end product.

In the journey towards a brighter and better future, we facilitate the entry of industry-sponsored research into Malaysia, working closely with the government and relevant authorities to ensure that all regulations and best practices are met.

In CRM, we credit the outstanding performance to the team we have anchored from within our organisation. Their endless pursuit of innovation and continuous improvement have propelled CRM forward to optimise the opportunities that come our way. In tandem with our passion for the clinical research landscape, we ensure core values of transparency, honesty, accountability and trustworthiness resonate throughout CRM. These qualities are also cascaded to our principal investigators and Study Coordinators, who act as the catalysts of the clinical research process.

As CRM vouches for an aspiring future in the clinical research industry, we have implemented mechanisms to expand hospital capacity for clinical trials and tests. This is possible by tapping into our vast talent pool consisting of principal investigators and medical assistants.

MINISTRY OF HEALTH MALAYSIA

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FROM THE CEO's DESK

The year 2017 took off to a good start with a Memorandum of Understanding between Clinical Research Malaysia and C&R Research Inc, Korea's largest contract research organization (CRO). C&R Research met us during the DIA 2016 Annual Meeting at Philadelphia where CRM was exhibiting; and the rest, as they say, is history. With this collaboration, we are hoping that more trials come to Malaysia while C&R Research can benefit from our support for their clinical projects.

Also this year, our poster abstracts were accepted and presented at the 29th DIA Euromeeting in Glasgow and the National Heart Association of Malaysia Annual Scientific Meeting. Do expect more of our abstracts to be featured at other local and international conferences as we strive to position Malaysia on the global clinical research map.

In this issue of the bulletin, I would like to take the opportunity to commend the Medical Research and Ethics Committee (MREC) for their efforts in reducing their approval timeline from 71 calendar days in 2014 to 53 calendar days in 2016. This improvement would mean a reduce in the overall timeline of when a study gets to be initiated at a clinical trial site, further making Malaysia a more attractive country among sponsors and CROs to conduct industry sponsored research (ISR).

Our very own investigators and research team have also made Malaysia proud by being one of the top five highest recruiter globally for the SOLAR study as of January 2017. This goes to show that to make Malaysia the preferred destination for clinical research in this region, all parties play an equally important role in working towards the common goal.

I shall leave the articles in this bulletin to speak for themselves. Have an enjoyable read and keep up the good work!

Contents

A thrust forward for Malaysia and South Korea in the clinical research industry

Petaling Jaya, 18 January 2017 – C&R Research Inc., Korea's largest contract research organization (CRO) and Clinical Research Malaysia (CRM) have signed a Memorandum of Understanding (MoU) to cooperate in promoting clinical trial activities in Malaysia and South Korea.

Malaysia has existing experience, facilities, processes, regulations and manpower in conducting clinical trials for over 20 years. With the current Malaysian Economic Transformation Program (ETP) that targets clinical research as one of its main drivers in economic growth, Malaysia has accelerated its efforts to reach out to foreign players in the clinical research field. With this cooperation, both parties will provide support and valuable resources to complement the needs of each country in terms of business development, clinical trial operations and trainings. Malaysia stands to benefit through business networking opportunities from South Korean pharmaceutical and biotech companies which may see more trial coming into the country. C&R Research Inc. will enjoy CRM's complementary feasibility services and support in clinical projects as well as in C&R's establishment in Malaysia.

The MoU ceremony was witnessed by the Director General of Health, Malaysia, YBhg. Datuk Dr. Noor Hisham, the Deputy Director General of Health (Research & Technical Support), YBhg. Datuk Dr. Shahnaz Murad, Director of the National Clinical Research Centre, Dr. Goh Pik Pin and Dr. Akhmal Yusof, the CEO of CRM. Also present was the Ambassador of the Republic of Korea, HE Dr. Yu Hyun-seok, Finance Attache Ambassador of the Republic of Korea, Mr. Park, Sang-il, KHIDI-ASEAN Director General, Mr. Lee Dong-won, KHIDI-ASEAN Researcher, Mr. Jung Yun-young and Chairman of C&R Research Inc., Mr Yoon Moon-tae. C&R Research Inc.

Gathering of Industry Players Under One Roof

Kuala Lumpur, 15 March 2017 – The recent Industry Dialogue organized by Clinical Research Malaysia set a good start for the year 2017 by gathering the stakeholders and industry players of the clinical research industry under one roof. This year's Dialogue saw speakers from the National Pharmaceutical Regulatory Agency (NPRA), the Medical Research and Ethics Committee and Dr. Chew Lee Ping from Sarawak General Hospital (SGH) updating the attendees with the recent changes in the regulatory environment as well as developments in the new CRC SGH. A total of 60 representatives attended the dialogue session. Datuk Dr. Shahnaz Murad, the Deputy Director General (Research & Technical Support) was present to give her Keynote Address. In her speech, she stressed the importance of the dialogue session and the need for the industry to leverage this platform created by CRM to gain more understanding on the local research environment and form strategic collaborations that will propel the nation forward towards being the hub for industry sponsored research by 2020.

Ramping up the I AM AWARE Roadshow

Kuala Lumpur, 23 March 2017 - It was a great turn-out at Hospital Kuala Lumpur (HKL) for the 'I am AWARE' Roadshow. 'I am AWARE' is a campaign to raise patient and public awareness of clinical trials. The focus will be on creating awareness and providing the necessary means for patients and the public to obtain information on clinical trials or to participate in any ongoing trials. Earlier last month, CRM held a pilot roadshow at Hospital Selayang and the team at Selayang managed to capture near to 100 registered patients/volunteers.

The nationwide campaign organised by CRM covers selected major hospitals and universities. This roadshow will lead up to the main event of the Clinical Trials Day later in May 2017. To date, roadshows have been conducted in several MOH hospitals and universities; Hospital Pulau Pinang, Hospital Umum Sarawak, USM and UNIMAS.

Clinical Trials Day is celebrated around the world on or near May 20 each year in order to celebrate the day that James Lind started what is often considered the first randomized clinical trial aboard a ship on May 20, 1747. This year, Malaysia will have its own Clinical Trials Day and it will be launched by the Minister of Health Malaysia. This event will be held at the National Cancer Institute (Institut Kanser Negara) on 16th May 2017. We will be celebrating the patients and volunteers that have participated in clinical trials.

CRM invites you to join this campaign to spread the awareness of clinical trials among friends and family. Visit www.clinicalresearch.my/iamaware for more info!

CRM - Good Clinical Practice Refresher Courses

Clinical Research Malaysia organizes several Good Clinical Practice (GCP) Refresher Courses throughout the year. The refresher courses gives participants the opportunity to reflect on their own practice within the context of recent developments in clinical research as well as utilizing real case examples.

The course will also guide participants to identify areas for improvements through common audit and inspection findings and the regulation of research to improve the quality of clinical trials.

GCP is the international ethical, scientific and practical standard to which all clinical research is conducted. Compliance with GCP provides public assurance that the rights, safety and wellbeing of research participants are protected and that research data are reliable.

To date, GCP refresher courses have been held at Perlis, Kuala Lumpur, Pahang and Perak. Moving forward to the second half of the year, the course will be held in Sabah, N. Sembilan, Kuala Lumpur and Johor.

NHAM-CRM Research Track 2017

Kuala Lumpur, 8 April 2017 – Clinical Research Malaysia (CRM) in collaboration with the National Heart Association of Malaysia (NHAM) organized a full day research track during the National Heart Association of Malaysia Annual Scientific Meeting 2017. The theme for this Research Track, "Discover, Collaborate, Translate" summarizes the objective of this initiative, which is to bridge basic sciences and translational research in the area of cardiovascular.

A total of 94 participants, 20 poster presenters, 15 oral presenters, 13 speakers and 9 judges contributed to the success of this track. The three prominent speakers for the three different plenary sessions were Prof Dato' Dr. Mohamed Isa, senior lecturer at the National Poison Centre, USM, Prof Datuk Paduka Dr. Wan Azman Wan Ahmad, Director of the Catheterization Laboratory of UMMC and Prof Dr. Gregory YH Lip, a Consultant Cardiologist and Professor of Cardiovascular Medicine at the Institute of Cardiovascular Sciences, University of Birmingham.

From 2011 to 2016, there was a total of 77 industry-sponsored cardiovascular studies being conducted in Malaysia, and for the last five years, cardiovascular studies have been in the top three most frequently conducted clinical trials in Malaysia. The idea of organizing the Research Track was conceived to foster relationships and collaborations among researchers with different areas of expertise besides providing a platform to exchange scientific ideas and inspire new research.

Winners for the Free Paper Session

Basic Science Category
Anand Ramalingam

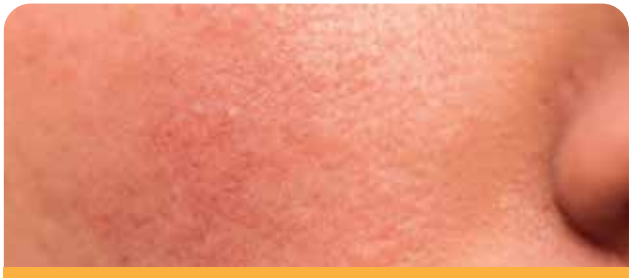
Bio Medical Category
Nurul Syafiqah Mohd Yusof

Public Health & Clinical Medicine Category
Chang Wei Lin

OncoMed sinks as cancer drug fails; Bayer opts against licensing drugs

OncoMed Pharmaceuticals Inc said it would discontinue a trial testing its experimental drug, demcizumab, as an initial therapy for advanced pancreatic cancer, after the addition of the drug to standard-of-care failed a mid-stage study. OncoMed's shares plummeted about 44 percent to $4.87 in premarket trading. The trial was testing demcizumab, Celgene Corp's Abraxane and chemotherapy versus a combination of Abraxane, chemotherapy and a placebo. The main goal was to slow disease progression.

Source: Reuters (April 10, 2017)



Here's What's Really Behind Your Acne Breakouts

About 85% of people get acne at some point in their lives, and scientists have long blamed it on the bacterium Propionibacterium acnes. But so-called P. acnes never entirely explained acne, because research has shown that it's abundant in hair follicles of people with clear skin, too—not just those with pimples. Now, new research puts forth a different potential acne culprit: an imbalance of bacteria living on the skin. The findings, presented recently at the Microbiology Society's Annual conference and published in the journal Scientific Reports, suggest that balancing bacteria—not wiping it out, as antibiotic treatments do—may be one future way to battle breakouts.

Source: TIME Magazine (April 10, 2017)

Taller, Bigger Women May Face Irregular Heartbeat Risk

Big or tall women are nearly three times as likely to develop the dangerous irregular heart rhythm known as atrial fibrillation as smaller women, a preliminary study says. The larger a woman's body size as a young adult, the more likely she is to develop the heart disorder later in life, according to the researchers. "There was a stepwise elevation in risk with increasing body size," said study author Dr. Annika Rosengren. "The group with the highest body surface area had nearly three times the risk as those with the lowest body surface area," added Rosengren, a professor of internal medicine at the University of Gothenburg in Sweden.

Source: HealthDay News (April 10, 2017)

Xanax, Valium May Boost Pneumonia Risk in Alzheimer's Patients

Alzheimer's patients given sedatives such as Valium or Xanax may have an increased risk for pneumonia, a new study warns. People with Alzheimer's disease are often given these drugs, called benzodiazepines, over the long term, the researchers said. Examples of benzodiazepines include alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan). The study found that people with Alzheimer's who took benzodiazepines were 30 percent more likely to develop pneumonia than those who weren't given the sedatives. The risk of pneumonia was highest in the first 30 days after starting the drugs, the findings showed.

Source: HealthDay News (April 10, 2017)

FDA warns Mylan over quality concerns at India facility

The U.S. Food and Drug Administration (FDA) has raised concerns over quality controls at a Mylan NV manufacturing plant in India, according to a warning letter from the agency dated April 3. India-based drug manufacturing facilities have been criticized by the FDA in recent years for violating quality standards, as the agency increases oversight of key suppliers to the United States. "Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture," the FDA said in the letter to Mylan.

Source: Reuters (April 11, 2017)

India's Strand Life Sciences launches blood test to detect cancer

A small Indian company launched on Tuesday a blood test to detect a wide range of cancers at a fraction of the cost of similar diagnostics available in the United States. Bengaluru-based Strand Life Sciences' test is designed to decode genetic information, which in turn will assist doctors to match patients with treatments most likely to help with their particular type of cancer - an approach that is increasingly becoming the medical norm. Strand's tests will be sold for 20,000 Indian rupees ($310), while similar technology in the United States costs more than $3,000.

Source: Reuters (April 11, 2017)

Thyroid Cancer Rates Raise New Concerns

Two new studies show that the high incidence of thyroid cancer may be more dangerous than previously thought. A study published in The Journal of the American Medical Association (JAMA) last month raises new questions about why thyroid cancer cases are on the rise. Data from a separate study points to flame retardants as a possible culprit. The research could cause a shift of doctors' and researchers' long-held beliefs that the fast-growing rate of thyroid cancer cases is solely due to unnecessary diagnoses involving small tumors that don't lead to death.

Source: Wall Street Journal (April 11, 2017)

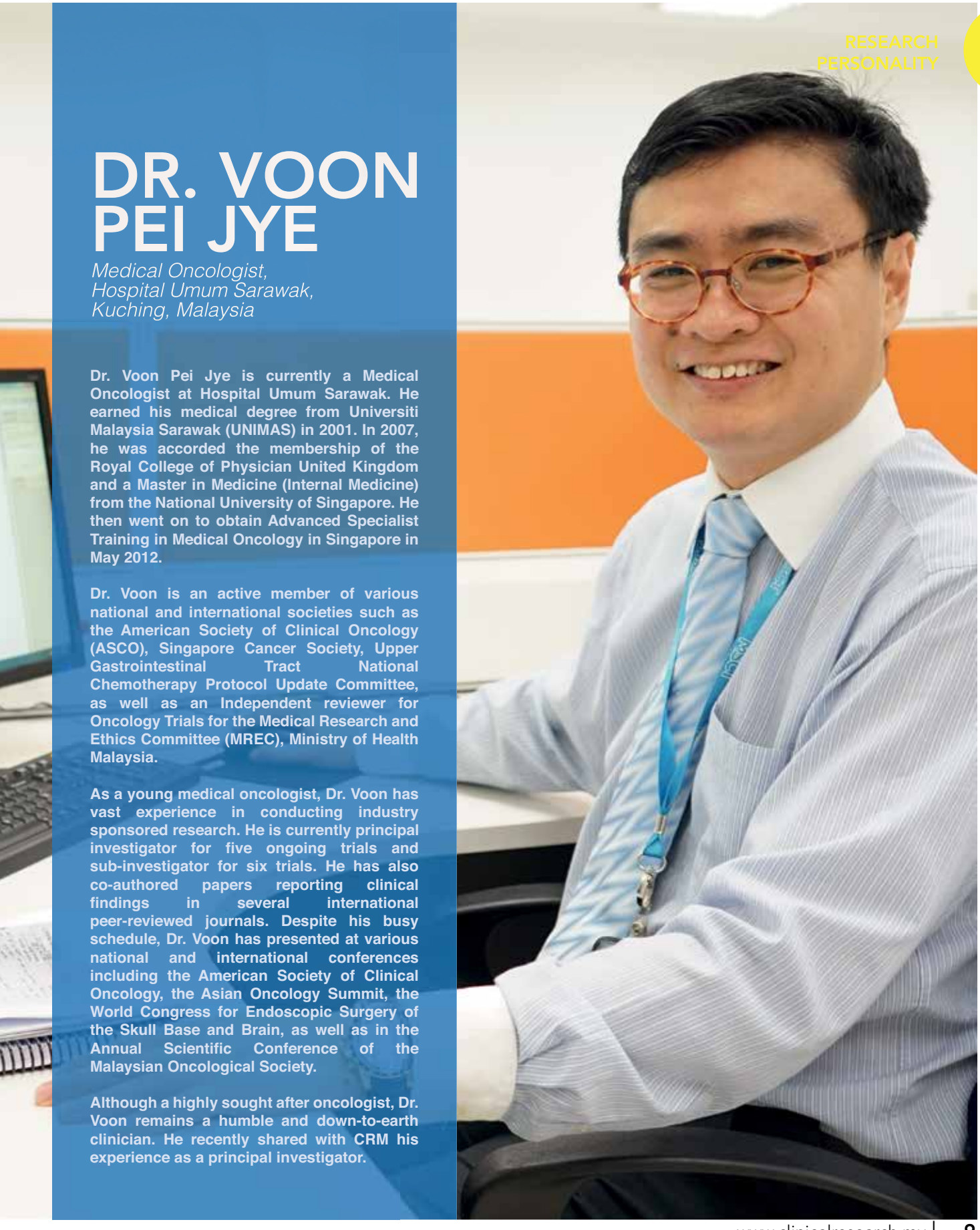
Roche's Alecensa notches trial win against Pfizer's Xalkori

Roche's Alecensa kept people with a specific lung cancer alive longer without their disease progressing than Pfizer's Xalkori, the Swiss drugmaker said on Monday, as it seeks to move in on the U.S. company's share of early treatment of the disease. Roche now plans to submit the results of the Phase III study to global health regulators, it said in its statement.

Source: Reuters (April 10, 2017)

DR. VOON PEI JYE

Medical Oncologist,
Hospital Umum Sarawak,
Kuching, Malaysia



Dr. Voon Pei Jye is currently a Medical Oncologist at Hospital Umum Sarawak. He earned his medical degree from Universiti Malaysia Sarawak (UNIMAS) in 2001. In 2007, he was accorded the membership of the Royal College of Physician United Kingdom and a Master in Medicine (Internal Medicine) from the National University of Singapore. He then went on to obtain Advanced Specialist Training in Medical Oncology in Singapore in May 2012.

Dr. Voon is an active member of various national and international societies such as the American Society of Clinical Oncology (ASCO), Singapore Cancer Society, Upper Gastrointestinal Tract National Chemotherapy Protocol Update Committee, as well as an Independent reviewer for Oncology Trials for the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

As a young medical oncologist, Dr. Voon has vast experience in conducting industry sponsored research. He is currently principal investigator for five ongoing trials and sub-investigator for six trials. He has also co-authored papers reporting clinical findings in several international peer-reviewed journals. Despite his busy schedule, Dr. Voon has presented at various national and international conferences including the American Society of Clinical Oncology, the Asian Oncology Summit, the World Congress for Endoscopic Surgery of the Skull Base and Brain, as well as in the Annual Scientific Conference of the Malaysian Oncological Society.

Although a highly sought after oncologist, Dr. Voon remains a humble and down-to-earth clinician. He recently shared with CRM his experience as a principal investigator.

Can you please tell us when and how did you first got involved in industry sponsored research?

Traditionally, Hospital Umum Sarawak has a robust landscape for clinical trials. I still remember clearly my medical officer days in our Cardiology Department, whereby we will have a daily early morning research meeting to update on the ongoing trials in the department. This was my initial exposure to industry sponsored research.

It was during my subspecialty training in Medical Oncology at the National University Hospital of Singapore (NUHS) that propelled my interest into clinical research. The breadth of experience and exposure that I encountered at this centre further consolidate my conviction on the importance of clinical trials as a cornerstone to the development of medicine in general and specifically for oncology.

How did clinical trials change your practice and management on patient care?

Essentially, the principles of our day to day clinical practice do not change with clinical trials as the guiding principle for clinical trial (ie. Good Clinical Practice) is in accordance to these pivotal principles. What clinical trials provide are extra options in the management of patients. These options are crucial in disciplines like oncology as treatment choices are always very limited especially in advanced stages. Such dire situation is further compounded by non-sustainable substantial cost of the latest oncology treatment. Thus, clinical trials provide invaluable access of potential drugs to patients who may otherwise have limited options for effective treatment.

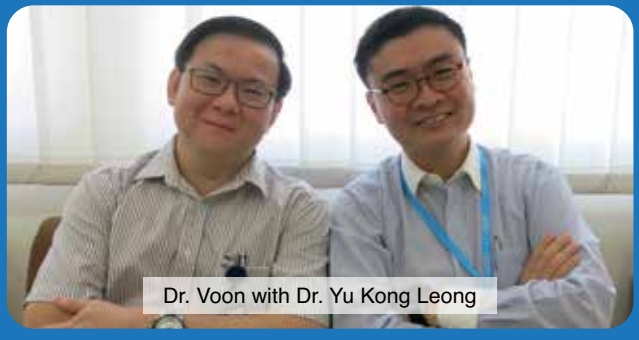
> ***"Diligence, dedication, perseverance and a never-give-up attitude are crucial when faced with difficulties in a trial"***
>
> ***- Dr. Voon Pei Jye***

There are many challenges faced by investigators during the course of a clinical trial. What would be your main challenge and how do you handle it?

Time. It is definitely the major challenge faced by majority of investigators in our country. I believe almost all investigators in Malaysia have their own clinical duty in addition to conducting clinical trials. As a result, most of the clinical trial activities are conducted outside normal working hours, for example during lunch breaks and after office hours. Hence, good time management especially in planning the daily activities ahead is essential in ensuring the smooth running of a particular trial without affecting the other duties of a clinician.

As an investigator, what is the most rewarding part of being in a clinical trial?

The ability to expand the access of treatment options to my patients, especially in Phase 3 trials whereby the standard therapy arm of the trial is too costly for patients to afford. Furthermore, participants in the trials may be the first few in the world to have access to the most advanced therapy that will only be available to others in a couple of years. In addition, participating in a clinical trial also provides a chance for clinicians to engage in the development of better drugs and treatment.



Dr. Voon with Dr. Yu Kong Leong

In your opinion, what type of attitude/s makes a good investigator?

Targets and timelines are very demanding especially for a clinician with other clinical duties. Thus, it is pivotal for investigators to be well disciplined in conducting clinical trials especially with the numerous targets and timeline that needs to be met. Besides, diligence, dedication, perseverance and a never-give-up attitude are crucial when faced with difficulties in a trial. A successful investigator should also be flexible and resourceful to look for alternative avenues in resolving any emerging issues.

You were recently named the highest recruiter globally for the SOLAR study. Can you share with us how you managed to achieve the high recruitment numbers? Any strategies involved?

One word. TEAMWORK! I owe it to all my dedicated team members that had made this coveted goal a reality. My team members range from co-investigators, study coordinators, pharmacists and nurses who have worked relentlessly to ensure the success of this trial. The key strategy is building a dedicated clinical research team that are able to work independently at the individual level but also as a team.

Back in 2014, there was only one dedicated study coordinator for oncology trials. During that time, more than 10 ongoing clinical trials were being conducted at our centre, ranging from phase 1b to phase 3. As we progressed, we rapidly expanded the team to four study coordinators over the span of three years.

We have to express our gratitude to CRM for providing us with study coordinators. In addition to working with our own team, we have been working closely with our colleagues in other disciplines including, radiology, pathology, pulmonology and surgery who

have contributed to the smooth running of the trials. Furthermore, we have been communicating effectively with contract research organizations and sponsors to resolve issues and ensure that the quality of the trials are constantly upheld. In summary, great team work and effective communication with others are the major elements in ensuring the success of a trial.

What drives your passion in clinical research?

Seeing our very own patients who have limited treatment options, having the same chance and opportunity to participate in trials which are being conducted in developed countries as well as in major cancer centres throughout the world is truly gratifying.

I personally feel that this is a tad bit that I can contribute to my patients, besides providing the daily conventional clinical services. Furthermore, the potential possibility of placing Hospital Umum Sarawak as an esteemed research center on the map for industry sponsored research also motivates our team to strive harder and better!

With the current services provided by CRM, how else do you think CRM can support investigators?

Firstly, I have to express my sincere gratitude to CRM in providing essential services in making industry sponsored research possible at our center. We definitely can't achieve our current milestone without the support from CRM. At this point, I think CRM has provided a comprehensive service that are holding the platform for industry sponsored research in this country. Nevertheless, I hope CRM will continue to provide more human resources support especially in increasing study coordinators to ensure clinical trials are executed with good quality. Study coordinators are the core element in the day to day running of a trial. Furthermore, CRM should increase training and support for new investigators and fledgling centres that are beginning to conduct clinical trials.

What changes/improvements would you wish to see being made by the policy makers to create a more conducive ecosystem for the conduct of clinical trials in Malaysia?

I wish the policy makers will be building an ecosystem that is looking into early phases of clinical trial including first in human trials. I believe this is the dream of most investigators everywhere, particularly if it is our own investigator initiated trials. I understand such move is ongoing and I hope a well-structured platform for these early phases trial will be ready soon. Furthermore, as time constraint is always the major limiting factor for investigators, a dedicated time for research should be encouraged especially for investigators who are overwhelmed by the day to day clinical duties. In addition, recognition and acknowledgement for successful investigators will be a positive incentive for those that have gone the extra mile in taking up the investigator's role.

What do you enjoy doing when you are not working?

During my leisure time, I love to travel and read. Both traveling and reading open my horizon and gives me a new perspective on life!

Dr. Voon with his research team at Sarawak General Hospital

Malaysia's Clinical Research Ecosystem

and the role of Clinical Research Malaysia in advancing industry-sponsored research in the country

By A.J.A. Ooi, K.F. Khalid, MD

This article was published in the January 2017 Issue of Applied Clinical Trials.

The impact of globalization resulted in the shift of industry-sponsored clinical research (ISR) from high economic countries to Eastern European, Latin American and Asian countries. Since 2008, Asia has shown significant growth in interventional studies with an average of 8% growth. Asian countries offer two main benefits for conducting clinical trials, which are its large and diverse patient pools, and the relatively lower cost of clinical trial conduct. Malaysia has many inherent qualities that make it an ideal country for conducting clinical trials such as a multi-ethnic population, which is relatively treatment naïve, competitive costs and an established healthcare infrastructure. Additionally, Malaysia has existing experience, facilities, processes, regulations and manpower in conducting clinical trials for over 20 years. The current Malaysian Economic Transformation Program (ETP) targets clinical research as one of its main drivers in economic growth. Therefore, the government of Malaysia, with an aim to promote and increase the number of clinical trials in Malaysia established Clinical Research Malaysia (CRM) in 2012 with the objectives of effectively increasing the speed, reliability and delivery of outcomes for all stakeholders involved. This review outlines the role of CRM, its achievements, future endeavors and the opportunities it provides for sponsors to carry out clinical trials in Malaysia.

Asia's Clinical Development Rise

Traditionally, ISR has been conducted in high-income countries in Europe and in the United States of America (USA) due to the

established research infrastructure and presence of major pharmaceutical companies in these countries.[1] However, globalization resulted in shifting ISR outside high income countries. The major beneficiaries of this shift have been Eastern European, Latin American and Asian countries. This change in the clinical research landscape, has substantially increased the number of registered clinical trials globally, as evidenced by two separate studies done analyzing the number of clinical trial registrations based off various global clinical trial registries. Viergever and Li analyzed the number of registered clinical trials based off the International Clinical Trial Registry Platform (ICTRP), which was established by the World Health Organization (WHO) in 2006. The database was mined to include all studies registered up to 31st December 2013. After excluding all observational studies, a total of 186,523 clinical trials from 16 clinical trial registries were included in the analysis. The number of registered clinical trials showed a substantial increase constituting a seven-fold rise between 2004-2013.[2] In another study conducted by Yathindranath et al, 15 online databases that contained registration for clinical trials globally and clinical trial registries in Asia were used. In Asia Pacific, clinical trial volumes have been steadily growing from 5.9% of the total global volume in 2005–2007 to 9.7% in 2011.[3] This shows that during these time periods, this region has become an important region for the clinical trial industry.

Asia specifically has shown significant growth in registered interventional clinical studies from 2008–2012 with an average growth rate of 8%,[4] whilst North America showed a decline of 2% during the same time frame.4 Sixty percent of the world population reside in Asia.[5] Therefore, as potential clinical trial hubs, Asian countries offer large and genetically diverse patient pools who are mostly treatment naïve, and a lower cost in conducting clinical trials in the face of limited patient pools and rising costs in the USA and Europe. Countries in Asia also offer varying disease epidemiology[5] in both infectious and chronic diseases due to the rise of lifestyle diseases such as diabetes, obesity, hypertension and various cancers due to urbanization.[3] Government interest in expanding clinical trial research, large hospital infrastructures and an increasing number of clinical researchers, growth in the pharmaceutical sector and an increase in investment in research and development by pharmaceutical companies also contribute to Asia being an attractive destination to conduct these studies.[3,5]

The Malaysian Economic Transformation Program

The government of Malaysia, with an aim to provide sustained growth in various economic sectors initiated the ETP which comprises 12 National Key Economic Areas (NKEA). Clinical research is listed under the Healthcare NKEA, the second among the Entry Point Projects (EPP2). Through this project, the government of Malaysia intends to promote clinical research in Malaysia and aims to increase the number of clinical trials from about 200 clinical trials per year to at least 1000 new and ongoing clinical trials by the year 2020.[6]

Malaysia

Malaysia comprises 13 states; 11 states in Peninsular Malaysia and two states Sabah and Sarawak, in the northern part of Borneo Island.7 Peninsular Malaysia is neighbored by Singapore in the south and Thailand to the north. The Ministry of Tourism tagline for Malaysia, "Malaysia truly Asia" depicts the diversity of races in this culturally rich land. The population estimates for 2016 stand at 31.7 million (107 males per 100 females) people out of which 89.7% are Malaysian citizens. Three major races and a minority of other races make up the Malaysian population (68.7% Bumiputera; consisting mainly of the Malay race, 23.4% Chinese, 7.0% Indians and 1% other races).[8]

The median age is 28 years and the largest age group, between 15-64 years, make up 69.4% of the population. The proportion of the elderly is also increasing due to better access to healthcare. Malaysia has a growing urban population. In 2016, the urban population is estimated at 75% of the total population (compared to 57% in the East Asia and Pacific region).[9]

Malaysian healthcare system

The healthcare system in Malaysia is two-pronged with a major contribution from the public health sector. Both public and private healthcare systems are closely monitored by the government under the Ministry of Health, and share a similar system that offers primary health and specialist care. The public health system is far reaching with presence in the rural and urban settings, while private healthcare is mainly found in the urban areas.

Malaysia's public health system is based on the World Health Organization's (WHO) district health system model.10 The larger district health clinics are managed by family medicine specialists and are self-contained with their own basic laboratories, and X-ray and ultrasound facilities. These district health clinics are capable of attending to both acute surgical and medical cases as well as following up patients with stable chronic diseases, in addition to providing maternal and child healthcare services. The smaller community clinics that are under the purview of these district health clinics are most often run exclusively by registered nurses and mid-wives who are trained to provide preventive maternal and child services including home visits.[10]

Primary care in the private healthcare system is provided by privately owned general practice (GP) clinics, stand-alone specialist clinics and outpatient specialist clinics in private hospitals. In 2008, there were an estimated 6,000–7,000 GP clinics and for every 10 primary care visits, 6 were to GP clinics. Some GP clinics, especially those who belong to a group practice have added facilities such as portable blood analyzers, and x-ray and ultrasound services.[11] GP clinics like the district health and community clinics are located in both urban and rural areas of the country.

In 2013, 40.2% of all hospitals in Malaysia (N=351) were categorized as public hospitals (this included Ministry of Health hospitals, university hospitals and Ministry of Defense hospitals) whilst 59.8% were private hospitals.[12] About 47.5% and 67.1% of the public and private hospitals respectively provide specialist services. Data from 2011 show an increasing trend in specialist care for example from 2010 to 2011 there were 3 additional hospitals providing oncology services (total of 58 hospitals in 2011) and 10 new hospitals started providing psychiatric care during the same time frame (total of 94 hospitals in 2011).

Malaysia's clinical research ecosystem

In recent years, Malaysia has been striving hard to utilize the opportunity created due to the shifting of clinical trial bases of the of the pharmaceutical industry to Asia.

Malaysia has inherent benefits to conduct clinical trials such as its large multi-ethnic population that offers genetic diversity, established and good public and private healthcare systems, a consistently increasing number of Good Clinical Practice (GCP) trained and compliant investigators and support staff, an established and comprehensive ethical review process by ethics committees, adherence to intellectual property rights (IPRs) and competitive trial costs compared to other Asian countries. Malaysia also boasts shorter regulatory and ethics approval timelines for ISR that are comparable with countries like Hong Kong, Japan, Singapore, Taiwan and South Korea (Table 1).[13]

Table 1. Regulatory timelines in Asia-Pacific

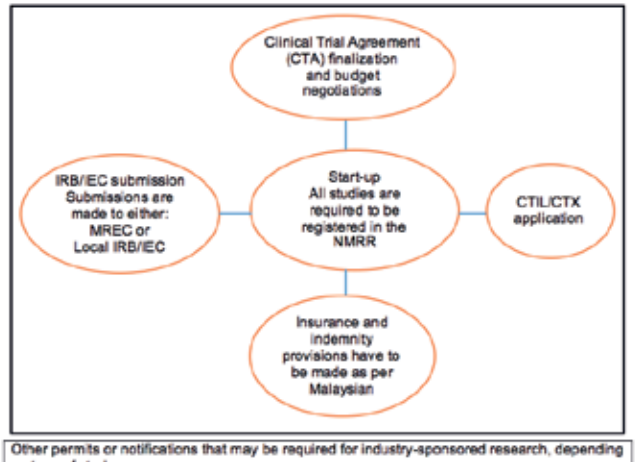
Countries	Timeline		Submission
	Regulatory	Ethics	
Singapore	Approx. 30 days	Approx. 30 days	Parallel
Malaysia	Approx. 30 business days	Approx. 50 business days	Parallel
South Korea	Approx. 30 days	Approx. 50 days	Parallel
Hong Kong	30–60 business days	30–60 days	Parallel
Japan	Approval is by default if no objections within 30 days	4–8 weeks	Sequential
Taiwan	Approx. 30 business days	Approx. 30–60 business days	Both

Generally, clinical research is conducted in Malaysia at university hospitals, Ministry of Health hospitals and increasingly at private medical centers across the country. The wide network of local Ministry of Health, health clinics represents a unique opportunity for access to a previously untapped, primary care patient pool.

The National Pharmaceutical Regulatory Agency (NPRA) ensures the quality, efficacy and safety of pharmaceuticals in Malaysia through the registration and licensing scheme. The NPRA acts as a Secretariat to the Drug Control Authority (DCA).[14] The DCA is empowered to review matters related to product registration, and approve or reject application for Clinical Trial Import License (CTIL) or Clinical Trial Exemption (CTX) among others. The IRB structure in Malaysia depends on the location or type of facility conducting the research. Generally, most university hospitals have their own local IRB/IEC, while research conducted at Ministry of Health hospitals fall under the purview of the central IRB, which is the Medical Research and Ethics Committee (MREC).[14]

CTIL/CTX applications are submitted to the NPRA following the Guidelines for Clinical Trial Import License (CTIL)/Clinical Trial Exemption (CTX). The NPRA screens the application dossier for completeness before handing them over to the DCA for a decision to be made. Once approval is granted by both the DCA and MREC (or other accepted IRB/IEC), the NPRA issues the CTIL/CTX and regulatory approval letters to begin the clinical trial (Figure 1).15 Generally, a CTIL/CTX application is processed within 30 working days while the MREC approval takes 50 working days, if no amendments to the submitted documents are required. Both CTIL/CTX and MREC applications can be submitted in parallel. Users (PI/CRO/Sponsor) who intend to submit to MREC (or other accepted IRB/IEC) 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.

Figure 1. The start-up process of industry-sponsored research in Malaysia



Other permits or notifications that may be required for industry-sponsored research, depending on type of study are:

Import/export permits for biological samples	Import permit for communication devices	Importation notification for medical devices
• Permits are required when the study involves either the importation or exportation of biological samples such as tumor biopsies, blood samples and urine samples. • Quantity of samples to be imported or exported has to be listed in the application.	• Permits are required if the study includes the importation of devices to be used in the study or at the study sites such as an eDiary.	• Importation notification is required if the study protocol includes the supply of medical devices to the study site that involve importing these devices (e.g., electrocardiogram, electroencephalogram and centrifuge equipment)

Source: Society of Clinical Research Professionals Malaysia

Clinical Research Malaysia

CRM is a non-profit company wholly owned by the Ministry of Health. CRM was established in June 2012 to position Malaysia as a preferred global destination for ISR and to function as an enabler and facilitator to the industry and medical fraternity for the conduct of clinical trials.

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 support and clear knowledge of the local research environment, CRM is able to provide sponsors and contract research organizations (CROs) with an extensive range of services that include complementary feasibility studies, investigator selection, placement and development of study coordinators, management of trial budget and review of clinical trial agreements.

Prior to CRM's inception, there were several challenges faced in the effort towards expanding the clinical research environment in the country. These hampered the operations of ISR in Malaysia in terms of speed, reliability and delivery of favorable outcomes to the relevant stakeholders. The challenges were the time consuming hiring process that involved government bureaucracy and acquisition of assets, poor transparency of fund management, and lack of activities to increase the number of investigators and well-equipped trial sites for the conduct of clinical trials. There was

also a need for a locally placed "one-stop" center to facilitate sponsors/CROs interested in conducting clinical research in Malaysia by championing collaborations with the regulatory agencies, customs officials and investment authorities. Furthermore, though the interest in clinical research among the existing investigators and support staff were high, there was no clear clinical research pathway to encourage and develop their potential in this area.

As part of Malaysia's ETP, CRM was established with the objectives of facilitating the conduct of clinical trials in Malaysia with the aims to ensure the reliability, speed and delivery of outcomes for all stakeholders. These objectives include the improvement of clinical trial sites by addressing their needs and allocating highly trained study coordinators, increasing well-trained and GCP compliant investigators through training and awareness campaigns, implementing strategies and procedures for feasibility assessments and investigator selection, providing transparent and efficient trial budget management, initiating collaborations with local, regional and global stakeholders, attracting global pharmaceutical and CRO investments, inspiring private hospitals and universities to be part of the expansion of the clinical trial environment, and investigating and addressing the perception and awareness of clinical trials among healthcare professionals, administrators, patients and the public.

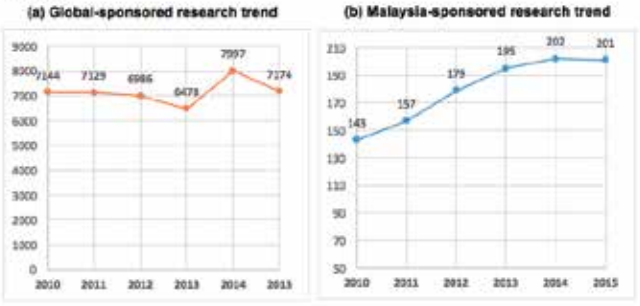
Achievements of CRM

CRM has developed five key strategies to put in place a comprehensive, enabling and supportive ecosystem that meet the needs of industry players and the medical fraternity. The five strategies are to grow the pool of investigators and sites, attract new ISR to Malaysia, collaborate with stakeholders, create awareness of CRM and develop human capital.

CRM is entrusted to compile and track the number of ISRs from MREC and all IRB/IECs and these numbers are reported annually to the Malaysian government. Between 2010 and 2015, Malaysia has seen a steady increase in the number of ISR from 143 trials to 201 trials within the five-year period (Figure 2). There was no increase in the number of trials between 2014 and 2015. During this time period, a global decline (by 10%) in the number of ISR was recorded, and Malaysia was also affected by it. The number of sponsors and CROs who utilized CRM's services however, recorded a sharp increase in 2016 compared to 2014. Up until September 2016, there was more than a 200% growth in the number of sponsors while the number of CROs doubled during this time period, indicating the confidence of foreign investors in Malaysia's capability in conducting ISR (Figure 3). In this same time frame, CRM's experience as a site manager has expanded to 25 therapeutic areas.

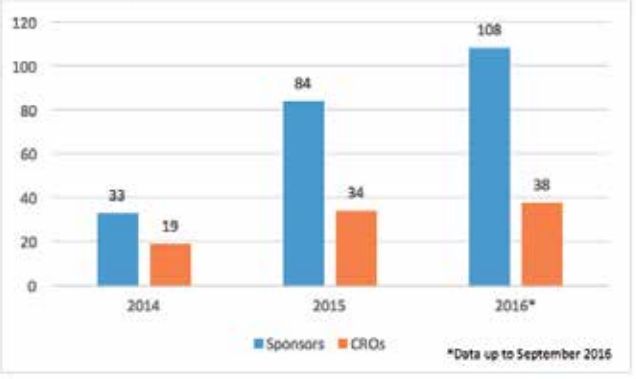
The gross national income (GNI) created by clinical trials in 2015 totaled over USD 28.01 million, an increase of USD 17.03 million from 2011. There was a growth in the number of Principal Investigators (PIs) between January and September 2016 (Figure 4) after the country recorded a sharp decline in 2015. One of the reasons for the decline was due to senior investigators leaving their services because of retirement with many of them not having put in place proper succession planning. Additionally, there was lack of support in promoting ISR to junior doctors during that time. It was in 2015 that CRM actively took up this role to increase the

Figure 2.



Source: (a) clinicaltrials.gov; (b) CRM data on file

Figure 3. Growth of sponsors and CROs



number of investigators by supporting 8 State Research Days in 2015 that saw an impressive 550 abstracts submitted from all over the country. Seeing its success, CRM has committed to support 11 of these State Research Days in 2016. State Research Day is a Ministry of Health initiative which is organized nationwide annually. Its aim is to provide an avenue and opportunity to the allied health and medical personnel to share their research findings, besides providing recognition and encouragement for them to engage in research. It is also a platform to raise awareness on the importance of research in improving patient care in the country.

In its infancy in 2012, CRM had 22 study coordinators that were placed throughout Malaysia at various sites conducting ISR and this number has grown to 93 study coordinators as of September 2016. CRM being true to its national agenda has expanded its operation beyond the realm of Ministry of Health sites. It has received requests to support investigators and sites in Ministry of Higher Education hospitals and private hospitals alike. The strategies employed by CRM had in 2015 created 1118 high skilled jobs in the clinical research industry in Malaysia, more than the 1000 it was entrusted to create by 2020.

Among the various initiatives taken so far by CRM to improve the clinical research ecosystem have been to recruit, train and develop Medical Officers into future investigators, invest in various clinical research sites by equipping these sites with the necessary infrastructure to conduct clinical trials, shortened the clinical trial agreement (CTA) review and approval timeline from 14 working days to 5 working days, seconded staff to the MREC and to the Medical Device Authority (MDA) to improve approval timelines and assist in queries from the industry, and formed partnerships with

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OVERVIEW

The NCCR 2017 together with the REACTA Forum 2017 aims to communicate the latest global developments in **precision medicine** and its implications on the future of healthcare in Malaysia and in Asia besides clinical trial developments and research collaborations.

By bringing together global experts and thought-leaders of industry, healthcare and academia from across various disciplines in research and technology, the conference will provide valuable insights in this exciting and incredible promise for superior healthcare and better patient outcome.

The conference examines how close we are in this new era of healthcare as well as developments in global clinical trials and research collaborations in Asia. Keynote address, plenaries and symposium sessions will run concurrently with an exhibition by clinical research industry partners as well as poster sessions. The conference will provide excellent networking opportunities between researchers in different countries and to form potential research collaborations.

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LEARN: Key challenges, opportunities and good practices that will advance healthcare delivery.

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- Collaborative Research in Asia
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Assoc. Prof. Dr. Lee Soo Chin - Singapore

Associate Director (Research) and Senior Consultant, Dept. of Haematology-Oncology National University Cancer Institute
Associate Professor, Cancer Science Institute of Singapore, National University Singapore

Precision Medicine in the Management of Cancer Risk in the Population

Prof. Dr. Teo Soo-Hwang - Malaysia

CEO of Cancer Research Malaysia

Precision Medicine: How we Encourage Innovation in Oncology

Koichi Miyazaki - Japan

Senior Director, Clinical Group, Asia Development Dept., R&D Division, Daiichi Sankyo Co., Ltd., Japan

Building a Global Clinical Trial Centre: KCGI Present and Future

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Chair of Korea Clinical Trials Global Initiative (KCGI), Ministry of Health and Welfare

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Call for Abstract: 15th February 2017
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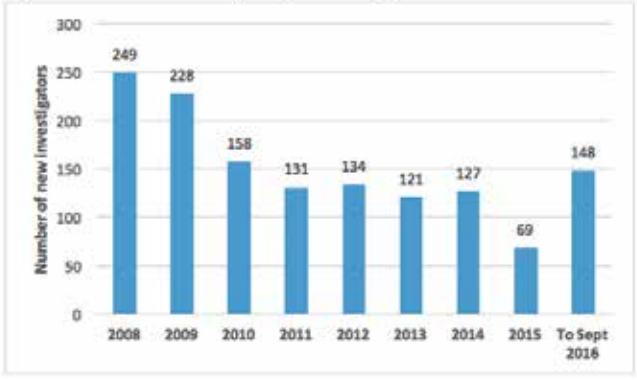
Figure 4. Number of new principal investigators



the media to create awareness of clinical trials. Furthermore, CRM organizes "Industry Dialogues" twice a year to understand and address issues being faced by the pharmaceutical, biotechnology and medical device industry as well as CROs.

CRM is currently in collaboration with the Drugs for Neglected Disease initiative (DNDi), a not-for-profit research and development organization that works to deliver new treatments for neglected diseases. With this project, CRM plans to develop a public health approach to hepatitis C within the framework of the future National Strategic Plan on viral hepatitis. The immediate goal of this initiative is to conduct clinical studies of promising new treatment regimens for hepatitis C which will be followed by scale-up of treatment for patients, with the overall objective of ensuring equitable access to affordable and effective treatments for patients suffering from this disease in Malaysia. A scale-up of treatment is necessary in order to have an impact on the number of cases, which are steadily increasing. Due to this surge in the number of cases and the high prices of new hepatitis C medicines, it has been almost impossible for the Malaysian government to provide access to treatment at the necessary scale. The trials conducted with the support of DNDi are anticipated to introduce a new therapy as soon as possible and a scale-up to reach all patients in Malaysia.

Overall, the strategies initiated by CRM from its inception in 2012 have been very encouraging. It achieved 94% of its key performance index 1 (KPI 1) determined by the number of ISRs conducted in Malaysia during the year 2015 (201 ISRs conducted vs. goal of 214 despite a 10% global decline). Meanwhile, the number of clinical trials performed in Ministry of Health facilities (KPI 2; 128/120) during the same year achieved 107% of its KPI 2.

Future endeavors of CRM

The Ministry of Health through CRM is driving an initiative to prepare Malaysia to conduct Phase I clinical trials in the next 3 years. This initiative, termed the Phase I Realization Project (P1RP) was design as the Malaysian government wishes to push its involvement in all phases of drug development. The 5 pillars that support the P1RP blueprint include the development of Phase I Guidelines, People Development, Capability Development, Preparation of Sites and Risk Management. The initiative that started in May 2016 will see the completion of the Phase I clinical research ecosystem in 2019. The capture of Phase I trials may resultresult in a spillover effect of more Phase II and III trials into Malaysia. Among the many economic advantages in opening Malaysia's doors to early phase studies include the transfer of knowledge and technologies to Malaysians, creation of new jobs in clinical research, spur local innovation and prevent outflow of investments. Conducting early phase studies in accordance with international regulatory standards would also drive capacity building for local ethical review, facilitate healthcare infrastructure development, increase economic activity by encouraging research into more innovative products and reduce the culture of dependency on developed countries.

Conclusion

Established by the Malaysian Ministry of Health in 2012, CRM exists to advance global health solutions for a brighter and more hopeful future for the people by providing speedy and reliable end-to-end clinical research support for quality studies.

CRMs innate understanding of the local clinical research landscape with the international standards of operations coupled with fundamental backing of the government ministries provides them with an incomparable advantage to work with partners from the nascent stages of development to materialization of the end product, in order to deliver better treatment and high skilled job opportunities.

Moving ahead, CRM plans to expand its horizons through P1RP to spur high impact Phase I clinical trials into Malaysia that may result in a spill-over effect of more later phased trials into the country. These accomplishments are taking Malaysia closer to the goal of being a 'globally preferred destination for clinical research'.

Funding sources

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CLINICAL RESEARCH CENTRE

SARAWAK GENERAL HOSPITAL

The new facility of Clinical Research Center Sarawak General Hospital (CRC SGH) was approved as an extension of the existing SGH in Kuching. The laying of the foundation stone commenced on 27th September 2007 by the Director General at that time, YBhg Tan Sri Dr Ismail Merican. The construction of the facility started on 15th January 2011 and completed on 10th July 2015. The new facility was handed over to end-user by the Secretary General of the Ministry of Health, YBhg. Datuk Dr. Chen Chaw Min on 19th July 2016.

CRC SGH started its operation from the new facility on 1st November 2016. Despite the new facility, CRC SGH will still keep the satellite site at Sarawak Heart Center which has a research ward that can accommodated up to 28 subjects for Bioavailability/Bioequivalence (BABE) studies. The new facility is expected to be operational at optimal capacity as a fully integrated clinical research platform by the fourth quarter of 2017. This facility will be a one-stop research facility to undertake both local and international clinical trials, especially for critical early phase clinical research (Phase 1 and 2), aiming for international accreditation for clinical, analytical, data handling and all other relevant aspects related to clinical trials.

Facilities

The new CRC SGH building consists of 3 floors; clinical, administrative and archiving floors.

Clinical (Level 4):

- **8 HDU beds, 2 ICU beds (with remote monitoring access)**
- **Physio Room equipped with each of the following instrument:**
  - » Cardiopulmonary Exercise Test (CPET)
  - » HOLTER
  - » Echocardiogram System
  - » Electroencephalogram System
  - » Stress Test Machine with Treadmill
  - » 24-hour Ambulatory Blood Pressure System
  - » Telemetry System
- **Laboratory**
  - » Clinical/ Biochemistry Lab
    - Clinical Dry Chemistry Analyzer with Ion Selective Electrode (ISE)
    - Clinical Chemistry – Immunoassay Analyzer (RIA)
    - Hematology Analyzer, 18Parameters/ 5PT DIF
    - Coagulation Analyzer
    - Urinalysis Particle Analyzer
    - HbA1c Analyzer
    - Blood Gas Analyser
    - Platelet Reactivity Analyzer
    - ESR Analyzer
    - ELISA system
    - Flow Cytometry
  - » Bioanalytical
    - Liquid chromatography tandem mass spectrometry (LC-MS/MS)
    - High performance liquid chromatography-diode array detector (HPLC-UV)
    - High performance liquid chromatography-fluorescence detector (HPLC-Fluorescence)
  - » Molecular complete with PCR equipment and Next Generation Sequencing (NGS)

There are also sufficient supporting equipment such as analytical balance, ultrapure water system, centrifuge, etc. to support the activities in the lab.

- 5 Clinics/Consultation Rooms
- Investigational Product Room with controlled access. Temperature monitored fridge also available for temperature sensitive investigational product (IP).
- Sample Processing Room for biosample handling and bioarchiving. All fridges (4oC) and freezers (-20oC and -80oC) are temperature controlled with continuous monitoring.
- Dedicated Pharmacy to supply medications to CRC ward and study subjects.

Administrative (Level 5):

- Meeting/ Conference Room with built-in projector
- Interview Rooms/ Small Discussion Rooms for research consultations
- Industry Hotdesk (provide a working space for monitoring visits, industry visitors etc.)
- Active Archive Room
- High speed Wi-Fi

Archiving (Level 6):

- Passive Archive for long term archiving after study closed out (water and fire proof)

ICU Facility

Services

a. Clinical studies from Phase Ib to Phase IV (both medicines and devices)
   - 28 bedded ward for BABE and studies of lower risk
   - HDU and ICU ward for early phase studies from Phase IB and studies of higher risk

b. Support industry sponsored research (ISR) and investigator initiated research (IIR) in terms of providing IP support, consultation room, usage of facilities in Physio Lab and bioarchiving. All fridges and freezers for IP and biosamples are temperature guarded.

c. Support IIR for laboratory related services from clinical to molecular analysis

d. Research Consultations: NMRR, biostatistics

e. Conduct research related training:
   - Good Clinical Practice (GCP) Certification Workshop
   - Basic and Advanced Biostatistics Workshop
   - Introduction to Clinical Research (ICR) Workshop
   - Questionnaire Validation Workshop
   - Instrument application and laboratory related workshop

In the near future, clinical studies and laboratory services will be available for Phase I to Phase IV (both medicines and devices). The CRC SGH laboratory will be a core lab for biosamples analysis in the region (estimated to obtain full accreditation for ISO 17025 and ISO 15189 in 2019).

Clinical Trials Strength at CRC SGH

The types of trial that can be conducted:

- Phases I to Phase IV ISR – (any discipline) as SGH is the only tertiary referral public hospital in Sarawak
- Any IIR that requires support of CRC facilities

Medical and Clinical Research Team

- CRC – 49 staff (2 specialists, 5 medical officers, 8 pharmacists, 20 research nurses, 3 PPKs, 9 research officers, 1 IT officer, 1 admin staff)
- CRM – 9 staff (2 assistant regional managers, 1 senior study coordinator, 3 study coordinator level 1 and 3 technical study coordinator – technically trained to support CRC SGH lab)

Procedure Room

Laboratory

HDU Beds

Physio Room

Overview of the
Medical Research & Ethics Committee's (MREC) Industry Sponsored Research (ISR) Performance Statistics, 2014 - 2016

Gurpreet K*, Asha T*, Sharina MN*
*Medical Research Ethics Unit, NIH Secretariat, Ministry of Health Malaysia

MREC was formally established in 2002, with the purpose of safe guarding the rights, welfare and safety of subjects participating in research in Ministry of Health (MOH) facilities. It is the sole ethics committee for Ministry of Health facilities and may act as an Independent Ethics Committee for facilities outside the MOH.

MREC receives both Industry Sponsored Research (ISR) as well as Investigator Initiated Research (IIR) submissions for ethical approval.

This article provides a summary of the MREC's performance in ISR studies for the past 3 years.

The number of ISR studies received by MREC for the past 3 years is shown in Figure 1.

While majority of all studies received by MREC is approved, a small percentage gets disapproved or withdrawn. Table 2 shows the outcome of new ISR studies submitted between 2014 and 2016.

Approximately 95% – 97% of ISR studies received by MREC are of clinical research. Many of the clinical research received are interventional clinical trials followed by as bioequivalence studies. Figure 3 illustrates the types of ISR research study submitted to MREC.

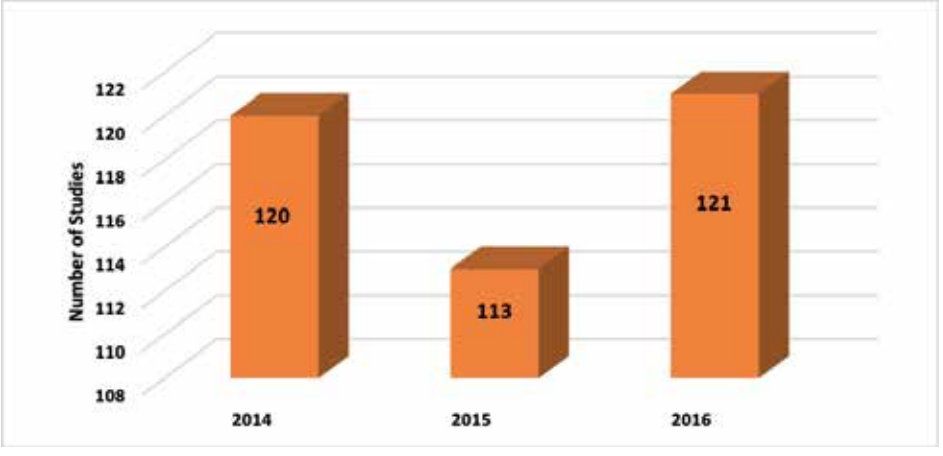


Figure 1: Number of New ISR studies received by MREC, 2014 - 2016

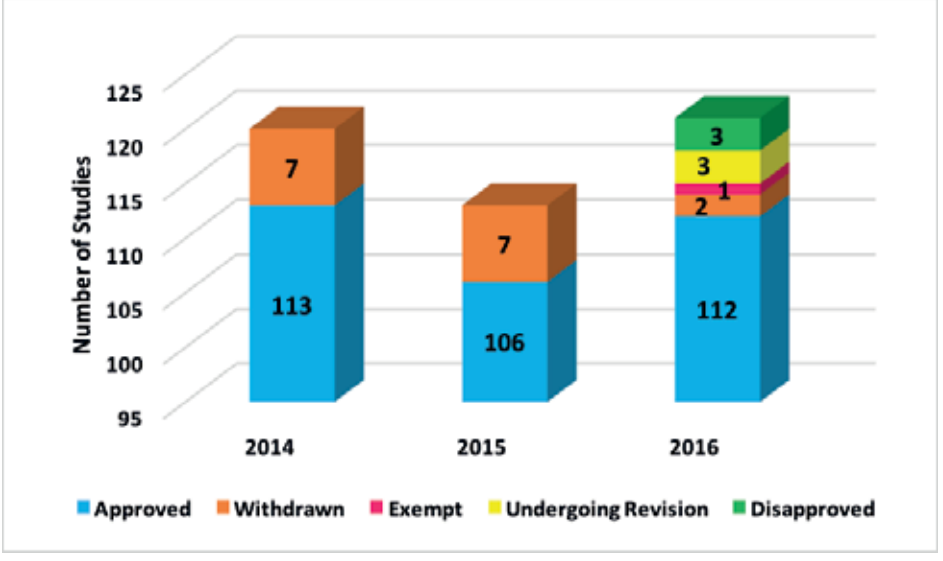


Figure 2: Outcome of New ISR Study Submissions, 2014 -2016 (as of 17 March 2017)

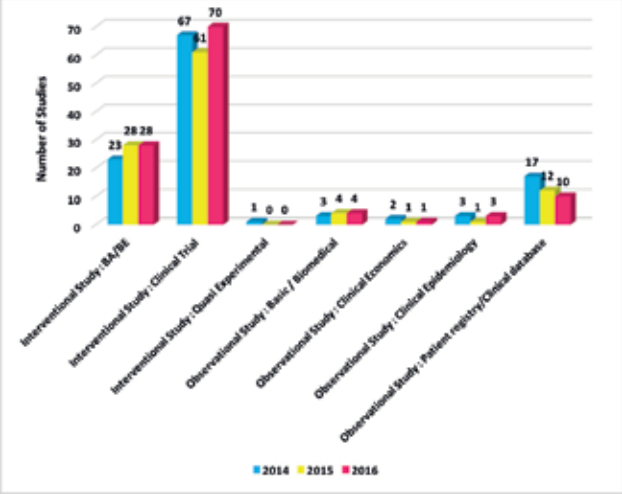


Figure 3: Types of ISR Research Submissions, 2014 -2106

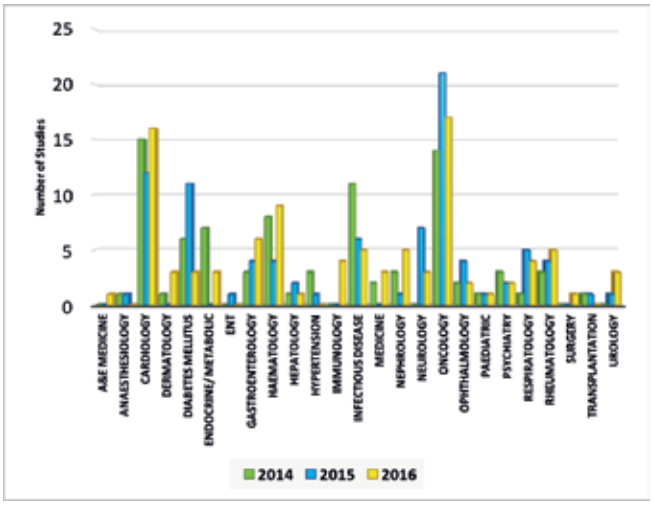


Figure 4: Therapeutic Areas of Research for ISR studies, 2014-2016

Approximately 95% – 97% of ISR studies received by MREC are of clinical research. Many of the clinical research received are interventional clinical trials followed by as bioequivalence studies. Figure 3 illustrates the types of ISR research study submitted to MREC.

A breakdown on the therapeutic area of the studies received showed that research in the area of Oncology and Cardiology topped the list. Other popular areas of research were Diabetes, Haematology, Gastroenterology and Infectious Disease (Figure 4).

80 – 90% of ISR studies received by MREC undergo full-board review, as majority of these studies are high risk studies based on risk benefit assessment (Figure 5).

With regards to approval timelines, the average approval timeline for ISR has improved significantly over the last few years and consistently remained under 60 days since 2015 (Figure 6). Some of the reasons for delayed approval timelines are as follows:

- Additional time requested by the investigator to respond to queries from MREC
- Additional review (additional meeting seating) & / revisions (more than one) required for high risk studies
- Additional scientific review period for stem cell & medical device studies by the respective Committees

In addition to reviewing initial applications, MREC also monitors approved studies until the study has been closed in all MREC approved sites. Most reports received by MREC are Protocol Deviation reports followed by Serious Adverse Event (SAE) reports. All reports received are reviewed before a decision is made on the study status. Details of post-approval activities conducted by MREC are in Figure 7.

Figure 5: Review Pathway for ISR studies, 2014-2016

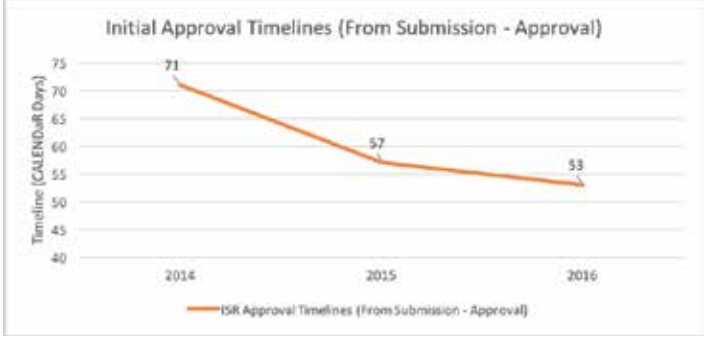


Figure 6: Approval Timeline for New ISR Studies, 2014 -2016

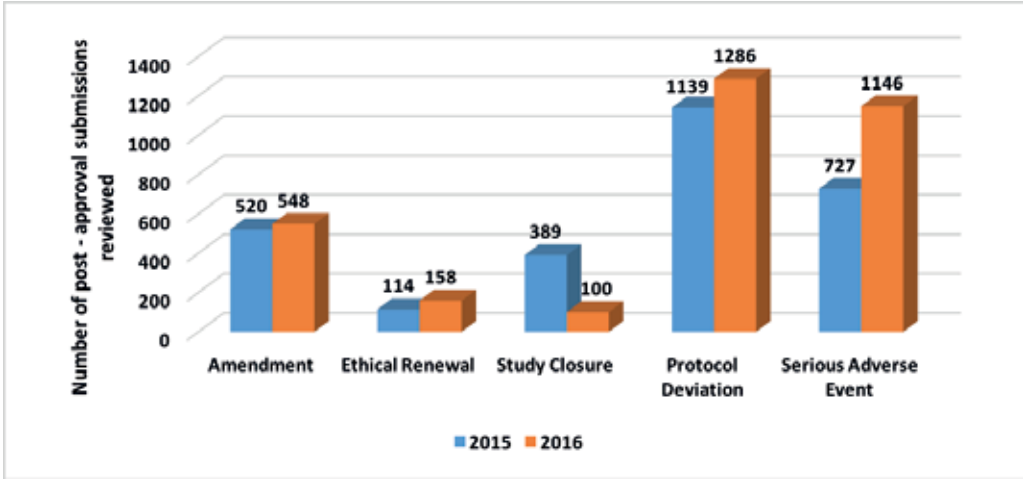


Figure 7: Post-Approval Continuous Review Activities, 2015-2016

For protocol deviations, the types of deviations reported range from administrative to more serious issues affecting the subject's rights, safety and wellbeing, such as incorrect informed consent process, recruiting ineligible subjects and administering the wrong IP / dosage. Serious protocol deviations may warrant warning letters to be issued to the Principle Investigator.

An in-depth analysis on the type of amendments approved by MREC in year 2016 is described in the below graph:

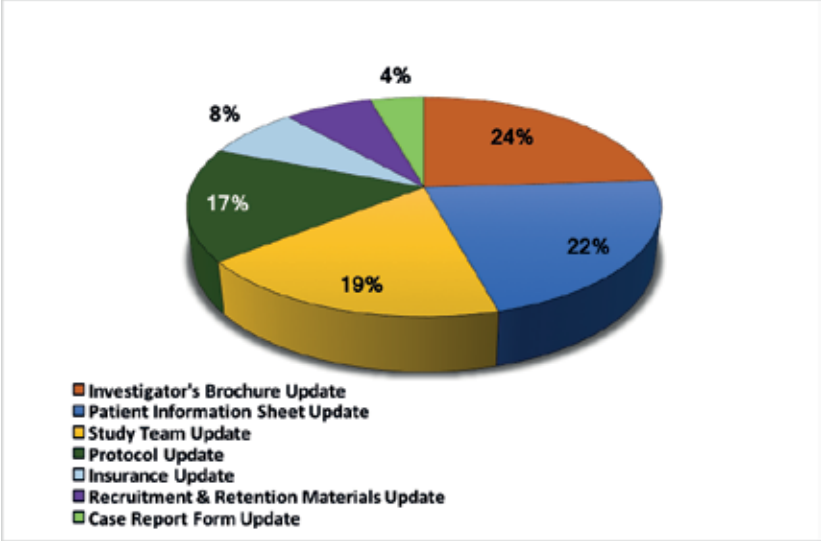


Figure 8: Breakdown on Types of Amendment Approved, 2016

As an accredited ethical committee, MREC is required to conduct compliance review as part of its responsibility / functions. As per MREC SOP there are 3 types of Compliance Review:

- Full Scope Review including inspection of the following: Essential Documents, Staffing & Infrastructure, Informed Consent Forms, Review of Patient Records, Review of SAE Reports & Review of Investigational Products.
- Limited Scope Review includes inspection of some of the elements mentioned above
- For Cause Review is triggered by receipt of serious complaint or concerns related to the study

MREC conducted its first full scope review of an ISR study in 2016. In future, MREC plans to conduct compliance reviews on a regular basis. Proper informed consent process and documentation are some of the areas that investigators need to pay attention to.

Biosimilars: Are they generics?

by Shaun Lee Chia Choon

Shaun Lee is an aspiring clinical research professional with an interest in drug safety and development. He graduated with a Masters of Pharmacy qualification from The University of Bath UK and at the time of writing, is a study coordinator at Kuala Lumpur Hospital.

The short answer is no and here is why.

Generics are conventionally small-molecule drugs, commonly produced via synthetic methods. They are interchangeable with the reference innovator products as their approval depends on the fulfilment of regulatory requirements to be both bioequivalent (comparable pharmacokinetics) and pharmaceutically equivalent (identical active substance). In other words, generics are therapeutically equivalent carbon copies of the reference innovator products.

In contrast, biosimilars (or "follow-on protein products" in the United States) are biological products which are highly similar, but not identical, to the reference innovator products for the approved indications. These pharmaceutical products contain active drug substances derived from living systems which are innately highly variable with regards to their post-translational modifications of proteins. In addition, the active substance of biological products generally consists of high molecular weight protein isoforms folded in specific three-dimensional configurations which are highly sensitive to changes. Consequently, there is increased probability of heterogeneity even between biological products of the same active ingredient and hence, a more comprehensive regulatory pathway is required for the approval of biosimilars compared to generic products.

REGULATORY APPROVAL OF BIOSIMILARS

Following the approval of the first biosimilar product (Omnitrope®) by the European Medicines Agency (EMA) in 2006, there have been many updates on the regulatory processes with regards to the approval of future biosimilars.

The United States Food and Drug Administration (FDA) uses a "totality-of-evidence" approach to approve biosimilars whereas the EMA uses a stepwise approach, which is the method adopted by the Malaysian regulatory body. Nevertheless, biosimilars are approved in both approaches upon demonstration of an absence of clinically significant differences in safety, quality and efficacy profile to the reference product. As a result, the approval pathways for biosimilars are generally more simple than novel biological products, with only selected nonclinical and clinical studies which are primarily comparative studies against reference innovator products.

In addition, the Malaysian regulatory authority imposes requirements for robust post marketing safety studies, particularly on the immunogenicity of certain biosimilars. This is in response to reported safety concerns including the development of antibodies that may attenuate the action of the biological product or neutralise the biological activity of endogenous proteins such as in the rare case of antibody-mediated pure red cell aplasia.

INTERCHANGEABILITY AND SUBSTITUTION POLICIES

Presently, the Malaysian regulatory authority does not permit the interchangeability and automatic substitution of biosimilars and reference products at the pharmacy level. In contrast, automatic substitution by pharmacists is permitted under Section 351(i) of the United States Public Health Service Act once a biosimilar is given an "interchangeable" status by the FDA. This is supported by a recently released draft guidance on the interchangeability of biological products by the FDA in January 2017, in line with the Biologics Price Competition and Innovation Act of 2009. While the EMA pioneered the approval of biosimilars, the agency does not have the authority to decide on the interchangeability status of biological products; this decision resides with the regulatory authorities in individual EU state members.

TAKE HOME MESSAGE

The development of biosimilars has increased treatment options at lower costs, thus, improving the access to medicines for a larger patient pool. However, healthcare professionals should be aware of the regulatory approval pathways and potential differences between biosimilars and the reference innovator products to make an informed treatment decision which is in the best interest of their patients.

About the "I AM AWARE" Campaign

The "I Am Aware" campaign is a public education programme about the importance of clinical trials. The campaign is initiated to promote understanding of the true benefits and risks of participation of clinical trials and to provide resources to help individuals make informed decisions about research involvement. Hence, we have organized activities such as roadshows on the proposed timeline as below.

Date	Location	Time
23 February 2017	Kuala Lumpur Hospital Selayang	8:30 am - 4:30 pm
23 March 2017	Kuala Lumpur Hospital Kuala Lumpur	8:30 am - 4:30 pm
27 March 2017	Penang Hospital Pulau Pinang	8:30 am - 4:30 pm
3 April 2017	Kelantan Hospital Raja Perempuan Zainab II	8:30 am - 4:30 pm
12 April 2017	Sarawak Hospital Umum Sarawak	8:30 am - 4:30 pm
25 April 2017	Perak Hospital Raja Permaisuri Bainun	8:30 am - 4:30 pm
28 April 2017	Kuala Lumpur Hospital Ampang	8:30 am - 4:30 pm
16 May 2017	Putrajaya Institut Kanser Negara	8:30 am - 4:30 pm

Campaign's Main Event

Understanding **Clinical Trials**

A clinical trial is an investigation of the effectiveness and safety of a new or improved medicine / treatment / medical device.

Clinical trials are an extremely vital process in advancing medical care and treatment. Carefully conducted clinical trials are the safest and fastest way to find treatments that work.

Who can participate in a clinical trial?

Each clinical trial has different eligibility criteria that you must fulfill in order to participate in the trial.

Clinical trials may require people with existing medical conditions or people who are healthy.

Questions to ask your clinical trial team before you participate:

- What is the purpose of this clinical trial?
- What exactly will happen to me during the clinical trial?
- Will there be any inconvenience or discomforts?
- Can I withdraw from the trial at anytime?
- How will this trial benefit me?
- How long will the clinical trial last?

Poster presented at the 29th DIA EuroMeeting 2017 at Glasgow, UK

The Common Reasons of Feasibility Study Rejections Among Malaysian Investigators and Corrective Measures Undertaken

Khairul F. Khalid, Audrey A.J.A. Ooi, W.C. Tay

Objective

To identify the common reasons of rejection of a feasibility study among investigators in Malaysia during feasibility assessments and corrective measures undertaken.

Method

Clinical Research Malaysia (CRM) provides a centralized feasibility service to local and international sponsors and contract research organizations intending to conduct clinical research in Malaysia. The centralized feasibility team at CRM receives feasibility questionnaires from these organizations before forwarding them to relevant investigators after performing a thorough analysis based on the central intelligence database of CRM.

A total of 178 feasibility questionnaires were given to investigators in Malaysia from January 2015 to December 2016 to assess their interest in taking up a clinical trial. The number of positive and negative responses were taken and their reasons for turning down a feasibility study was recorded.

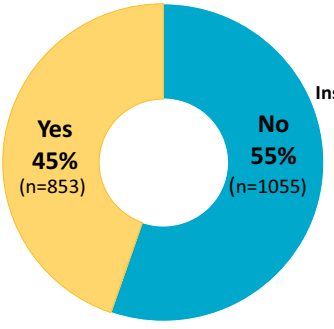
Results

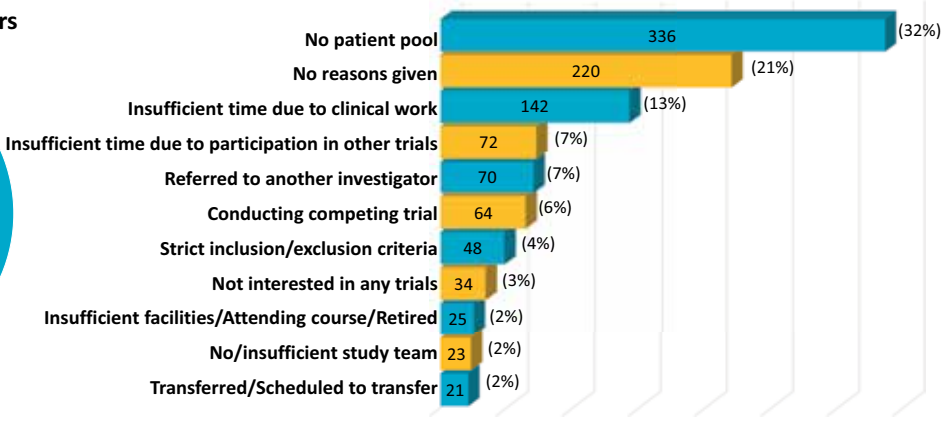
Out of a total of 1908 responses received in this time period, 853 investigators agreed to participate in a clinical trial while 1055 declined. The reasons for declining to participate were obtained and these reasons were categorized into 11 different categories.

The majority which made up to almost one third (n=336) of the reasons for turning down a feasibility study was the lack of patient pool. Insufficient time due to clinical work made up 13% of the overall rejection reasons, and this was followed by 7% citing insufficient time due to participation in other trials, 6% conducting competing trials and 7% referred to another investigator.

A smaller fraction of 4% turned down feasibility studies due to the strict inclusion/exclusion criteria of a trial, 3% were not interested in any trials, 2% had no/insufficient study team and 2% were transferred/scheduled to transfer to another hospital. Among the less common reasons given were insufficient facility at their site, planning to further studies/attend short courses and have already retired (3%). About 21% of investigators that were approached did not cite any reasons.

Responses from Investigators





Conclusion

Feasibility assessments are a valuable tool in clinical research for a pharmaceutical organization or contract research organization (CROs) to evaluate the possibility of conducting a particular clinical trial in a particular country. Analysis of the feasibility questionnaire feedback by investigators are an important measure to understand the local clinical research environment.

Based on the analysis of the results, the lack of patient pool and insufficient time to conduct clinical trial was the most common reasons given by investigators for rejecting feasibilities studies. To address this, the sites were mapped based on disease-specific patients that are available to enable the right site to be approached for the appropriate patient pool in future. Mapping was also conducted to track investigators who were saturated with clinical trials, those who were conducting competing trials and those that have been transferred so that only available investigators will be approached in the near future.

Other reasons that should be recognized include insufficient study team members, inadequate facilities and the lack of interest in taking up a clinical trial. Based on the results obtained, the Ministry of Health Malaysia had undertaken several strategies to develop a supportive and thriving clinical research ecosystem in the country. This include allocating protected time/policies for investigators to conduct trials, equipping the sites with the relevant facilities and raising awareness of clinical trials amongst the public and healthcare professionals.

These initiatives were carried out by Clinical Research Malaysia (CRM), a non-profit company wholly-owned by the Government of Malaysia that provides speedy and reliable end-to-end clinical research support to clinical research sites, investigators and the industry.
While these reasons may be common in countries conducting clinical trials, the proportion may differ based on the local research environment of a particular country. Understanding these reasons from investigators who are the core backbone of a clinical trial is vital in developing initiatives that may help in increasing the possibility of trial uptake in Malaysia.

Reference

A.J.A. Ooi, K.F. Khalid, Malaysia's Clinical Research Ecosystem, ***Applied Clinical Trials,*** *Jan 2017*

Poster presented at the 21st NHAM Annual Scientific Meeting 2017

PP 65

Trends in Industry-Sponsored Cardiovascular Clinical Trials in Malaysia

Tay Wai Cheng, Clinical Research Malaysia
Khairul F. Khalid, Audrey J.A. Ooi, Intan M.M. Murad, Clinical Research Malaysia

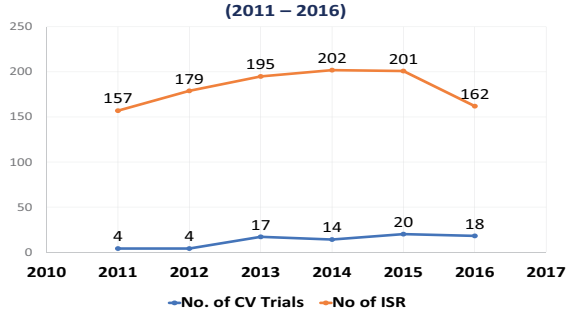
INTRODUCTION & OBJECTIVE

In the past two decades, clinical trials in cardiovascular disease have increased in number, size and quality to address the growing needs of new and improved cardiovascular treatments. Since 2011, Malaysia has seen a rapid growth in the number of cardiovascular industry-sponsored research due to the changing clinical research landscape in the country. While there have been reports on the types of industry-sponsored cardiovascular studies conducted globally, there has not been a report on country-specific data for Malaysia. This report displays the trend and characteristics of industry-sponsored cardiovascular studies conducted in Malaysia from 2011 to 2016.

METHODS

The total number of approved industry sponsored research (ISR) in Malaysia between 2011 to 2016 was compiled from all thirteen ethics committees (ECs) in Malaysia. Cardiovascular studies were extracted from the list of total industry sponsored studies and they were characterize according to its types, phases and indications.

TRENDS IN CARDIOVASCULAR INDUSTRY SPONSORED STUDIES IN MALAYSIA (2011 – 2016)



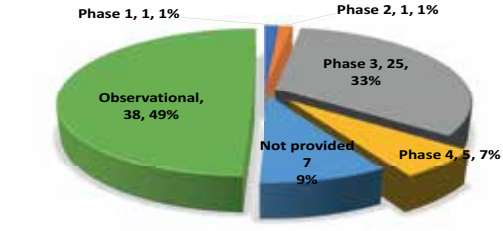
RESULTS

From 2011 to 2016, there is an upward trend in the total number of industry sponsored cardiovascular studies, in line with the overall trend of Industry Sponsored Studies in Malaysia. During this time period, a growth of more than three times from its initial number in 2011 was observed, with the highest being 20 studies in 2015.

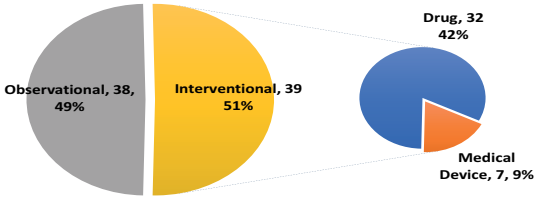
A total of 77 industry sponsored cardiovascular studies were conducted in Malaysia. About 49% were observational studies and 51% were interventional studies. Of the total number of interventional studies, 42% were drug-related, while the remaining 9% involved medical device. Interventional trials conducted in Malaysia were predominantly Phase III (33%) trials, followed by Phase IV (7%), Phase II (1%) and Phase I (1%). About 9% of the trials did not have information on the its phase. Across all 6 years, interventional studies outnumbered observational studies, except in 2014 and 2016. The highest number of interventional studies was seen in 2015 (13), while the highest number of observational studies was seen in 2016 (13).

By indication, ischemic heart disease recorded the highest number of cardiovascular studies (41%), followed by heart failure (14%), arrhythmia (12%), hyperlipidemia (8%), thromboembolic disease (5%), primary prevention (4%), valvular heart disease (3%), peripheral vascular disease (3%) and cardiomyopathy (1%). About 9% of studies were categorized under 'other' indications and this include those with multiple indications per trial, registries, as well as those where information was not provided.

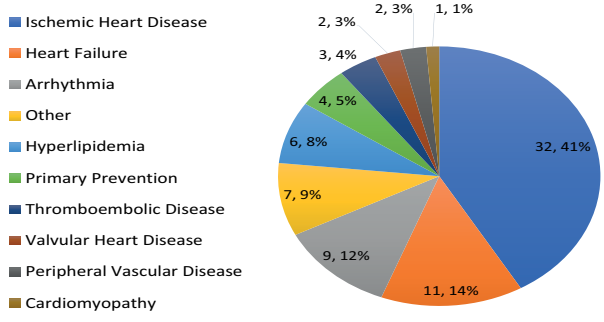
CARDIOVASCULAR STUDIES BY PHASE (N=77)



INTERVENTIONAL vs OBSERVATIONAL CARDIOVASCULAR STUDIES (N=77)



INDUSTRY SPONSORED CARDIOVASCULAR STUDIES BY INDICATION (N=77)



CONCLUSION

We observed an increase in the volume of cardiovascular trials, explained by the efforts undertaken by the Malaysian Government to improve the local clinical research ecosystem through the establishment of Clinical Research Malaysia (CRM), a non-profit company that provides speedy and reliable end-to-end clinical research support to clinical research sites, investigators and the industry. CRM has executed various strategies to improve Malaysia's capability to conduct clinical research to cater to the pipeline of new drugs/medical device from the industry.

This report highlights Malaysia's capability and participation in industry sponsored research (ISR) throughout the years. It is a useful source of information for pharmaceutical and medical device companies, investigators as well as patients seeking an overview of industry sponsored cardiovascular studies in Malaysia. We hope this publication will spur more ISRs to be conducted in Malaysia.

Contact: Tay Wai Cheng, taywc@clinicalresearch.my (Clinical Research Malaysia)

CRM bulletin

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The CRM Bulletin is published three times a year with a print run of 3000 copies per issue. These are delivered complimentary to a local and foreign readership base comprising of: Doctors and investigators (public and private); Hospitals (public and private); Sponsors and CROs; Universities and academics involved in clinical research; Medical research centres; Senior government and MOH officials; Clinical Research Centre (CRC) staff and investigators; Ethics Committees, Patient support groups; and selected medical schools.

The print run is complemented by an online subscriber base of 2000 readers currently, who receive an online copy of the CRM Bulletin.

The bulletin's objectives are to spread awareness about Malaysia's capabilities in industry sponsored clinical research (ISR), inform and attract industry players to Malaysia, motivate and educate potential investigators and support staff, build public awareness about the importance of clinical research, and finally serve as a forum to share news and development relevant to all stakeholders.

OTHER PUBLICATIONS BY CRM

Guide to BA/ BE Centres in Malaysia

Malaysian Guide on the use of Human Biological Samples for Research

NCCR bulletin

Guide for Industry

Patient Brochure

CRM in Photos


Meeting with IVD, DNDi & FIND, 11th Jan


IMR Wolbachia Laboratory Launching Event, 17th Jan


MoU Signing between CRM and C&R Research Inc., 18th Jan


Meeting with IVD, DNDi & FIND, 11th Jan


DNDi & Pharco Pharma meeting with Minister of Health Malaysia, 7th Feb


Visit to Zuellig Pharma Central Distribution Centre, 14th Feb


Investigator meeting with Aurigene, 15th Feb


I Am Aware Roadshow: Hospital Selayang, 23rd Feb


Visit to The Christie NHS Foundation Trust Manchester, 31st Mar


CRM Industry Dialogue 2017/1, 15th Mar


CRC-CRM-Quintiles Prime Sites Network 1st JSC Meeting, 22nd Mar

I Am Aware Roadshow: Hospital KL, 23rd Mar


I Am Aware Roadshow: Hospital Pulau Pinang, 27th Mar


CRM's Board of Directors Meeting, 27th Mar


I Am Aware Campus Roadshow: University Sains Malaysia (USM), 28th Mar


DIA Euro Meeting 2017, 29th - 31st Mar


I AM AWARE Roadshow: HRPZ II, 3rd Apr


NHAM 2017, 7th - 9th Apr


NHAM-CRM Research Track 2017, 8th Apr


I AM AWARE Campus Roadshow: UNIMAS, 11th Apr

I AM AWARE Roadshow: Hospital Umum Sarawak, 12 Apr

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