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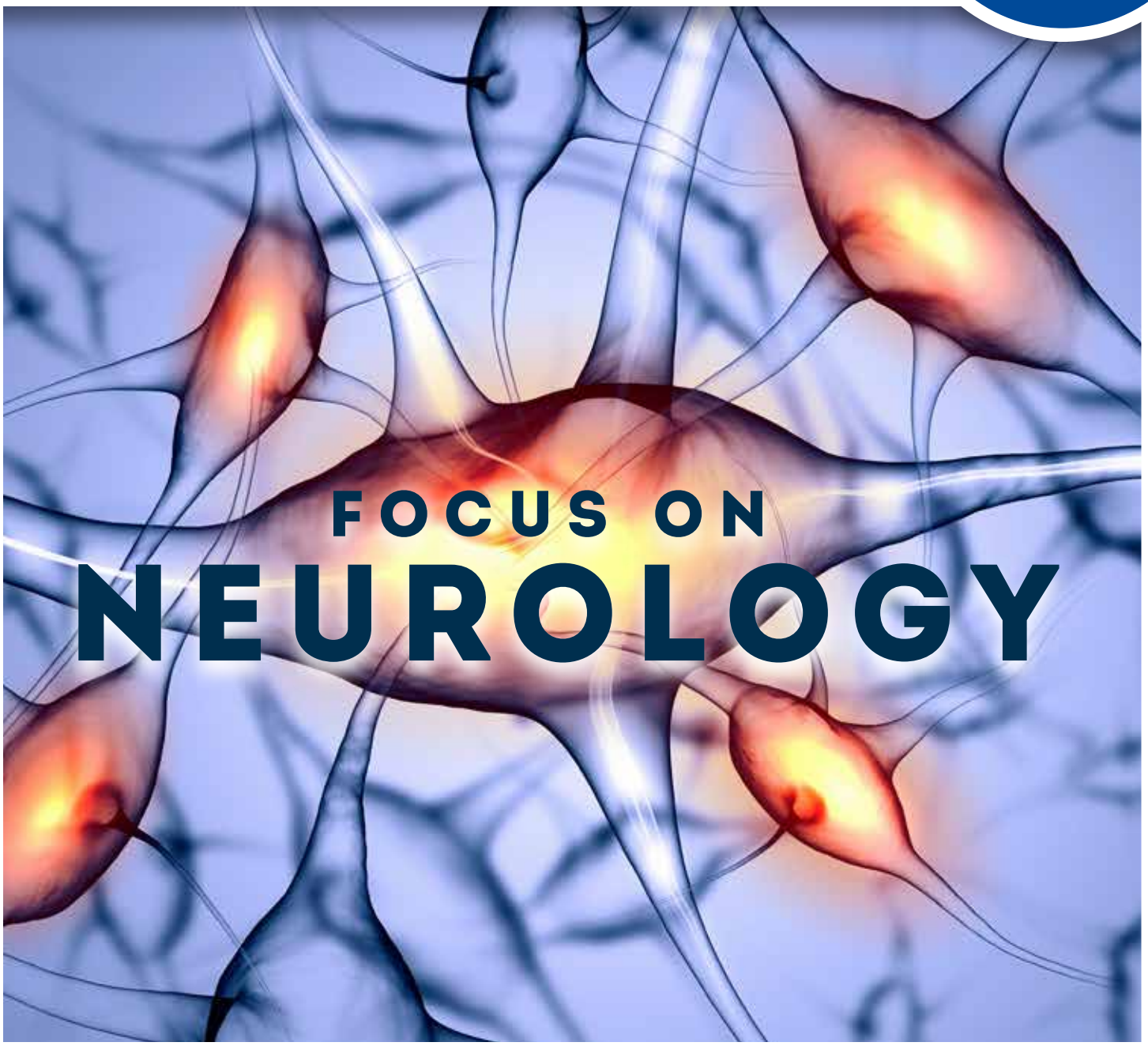

FOCUS ON NEUROLOGY

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CRM CLINICAL RESEARCH MALAYSIA *Your Global Solutions in One Nation*

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CRM
CLINICAL RESEARCH MALAYSIA
Your Global Solutions in One Nation

From the **CEO's** *desk*

It is with great excitement and commitment that I welcome the amazing opportunity of serving as the CEO of Clinical Research Malaysia. I certainly look forward to be of service to all stakeholders engaged in clinical research, but especially to our investigators and sites and to the industry players that commission and undertake clinical research.

It is rather an exciting time to be joining CRM. Great strides have been taken over the past two and half years to improve the quality and scope of our services and our effectiveness and support to all stakeholders. Nonetheless, a lot more remains to be done and I am sure I will have my hands full in raising CRM to greater heights.

Over the coming year, we will embark upon several new initiatives to turn CRM into an even more efficient and dynamic organization that can anticipate in advance the needs of our stakeholders and provide them with the necessary solutions and support. To summarize, CRM's strategy will be to focus on five key actions which are listed below:

- We will keep growing the pool of investigators and site;
- We will keep attracting new ISR to Malaysia;
- We will enhance cooperation with industry players and with the Clinical Research Centre Network;
- We will keep growing awareness and support among industry players, medical fraternity, the public and patients;
- We will intensively develop human capital in CRM.

The objectives of the above-mentioned strategies are to put in place a comprehensive, enabling and supportive ecosystem that meets the needs of industry players and investigators, and thereby accelerate the development of a thriving clinical research industry in Malaysia.

The building blocks towards this goal are already well in place and we welcome industry players and investigators to discuss with us on how they can tap into what Malaysia has to offer.

I am confident that together, we can meet the challenges ahead and achieve what the Government of Malaysia has entrusted CRM to achieve. I look forward to working with you and I sincerely believe that we can "Win as One Team".

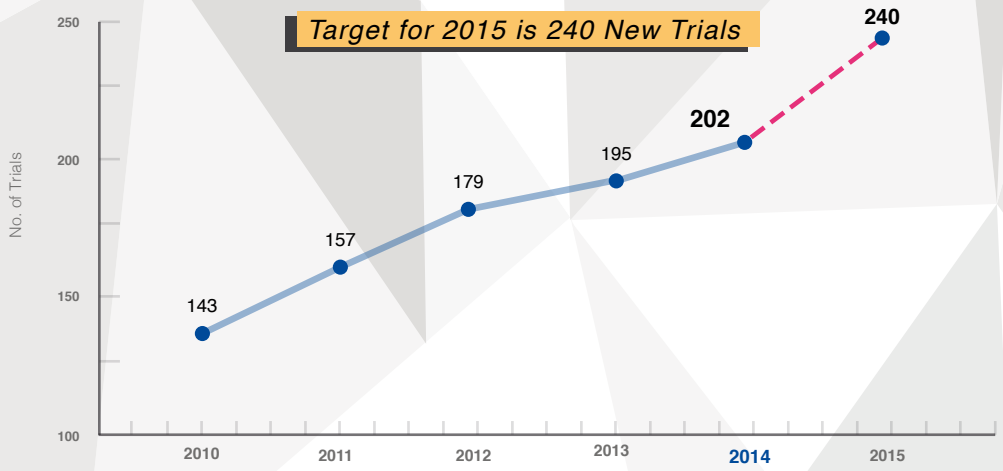
Watch the interview on YouTube

Dr. Akhmal Yusof
Chief Executive Officer
Clinical Research Malaysia
akhmal.yusof@clinicalresearch.my

2014 ISR STATISTICS

New ISR Approved by IRBs in 2014

202 new ISR trials were approved in 2014 by the IRBs. This amounted to 90% of CRM's 2014 KPI. The KPI target for 2015 is **240** new trials.

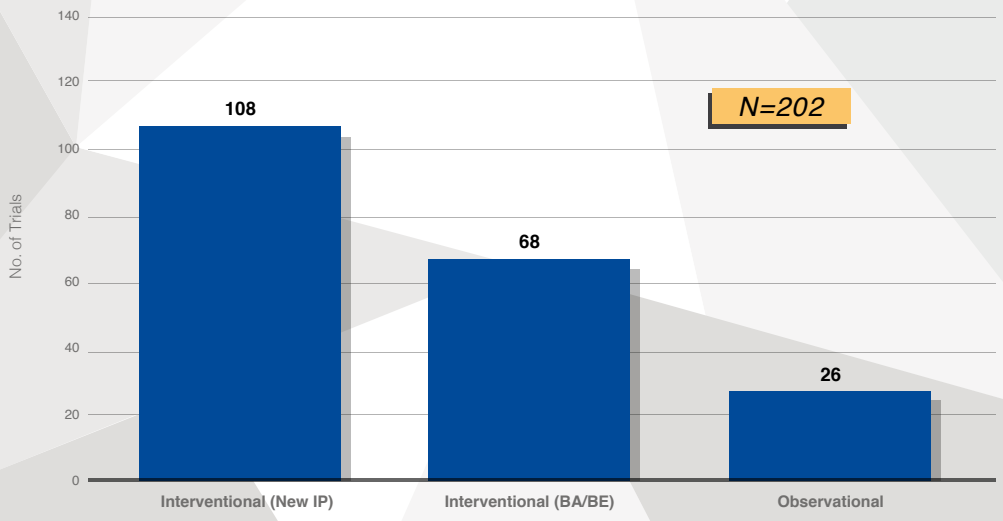


2014 Approved ISR by Classification

108 new interventional trials (including 10 medical device trials) were approved in 2014. This was followed by 68 BA/BE trials and 26 observational studies.

Note: BA/BE trials are separated in the major classification of trials as they are conducted to compare bioequivalence of IP and comparator and may be conducted in patients or in healthy volunteer subjects.

The category of trial (interventional & observational) follows the guideline as provided by FDA.

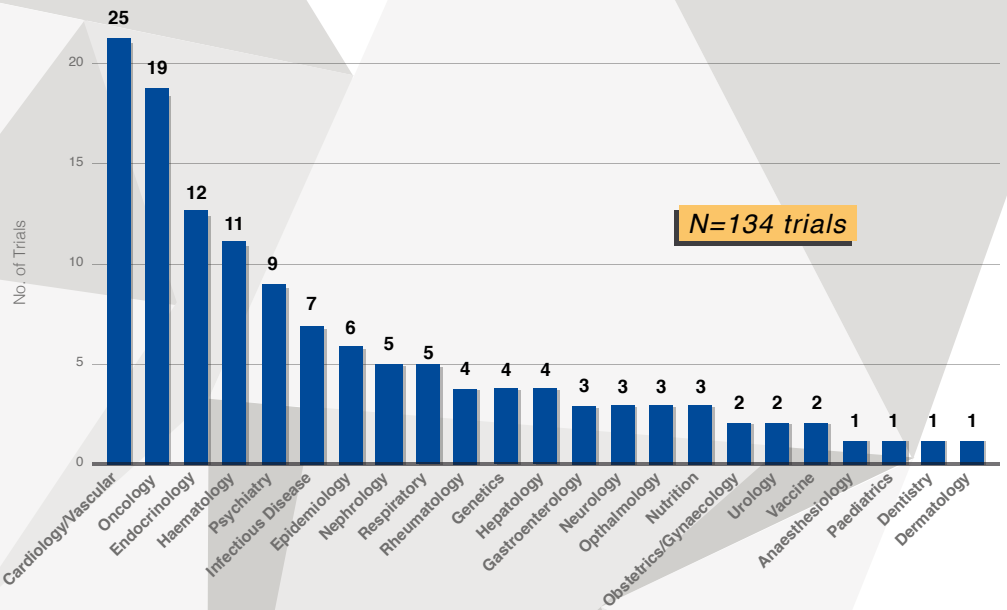


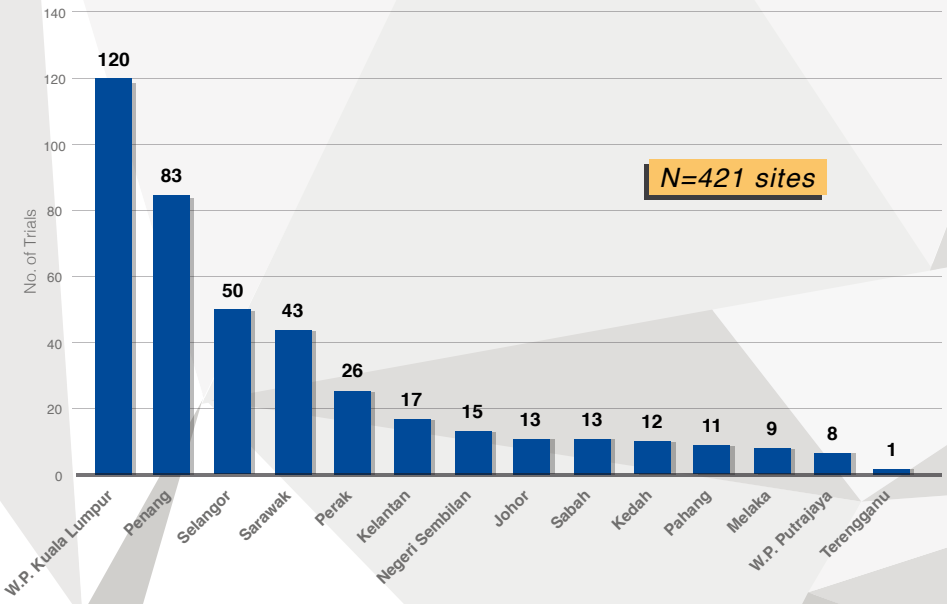
New Interventional & Observational ISR Trials in 2014

Cardiology/vascular accounted for 25 trials, followed by oncology wtih 19 trials and endocrinology with 12 trials.

10 new medical device trials were approved in 2014, of which 5 trials were for cardiology/vascular, 2 trials for nephrology and 1 each trial for ENT, infectious diseases and endocrinology.

Note: The therapeutic clasification follows the guideline as provided by FDA.

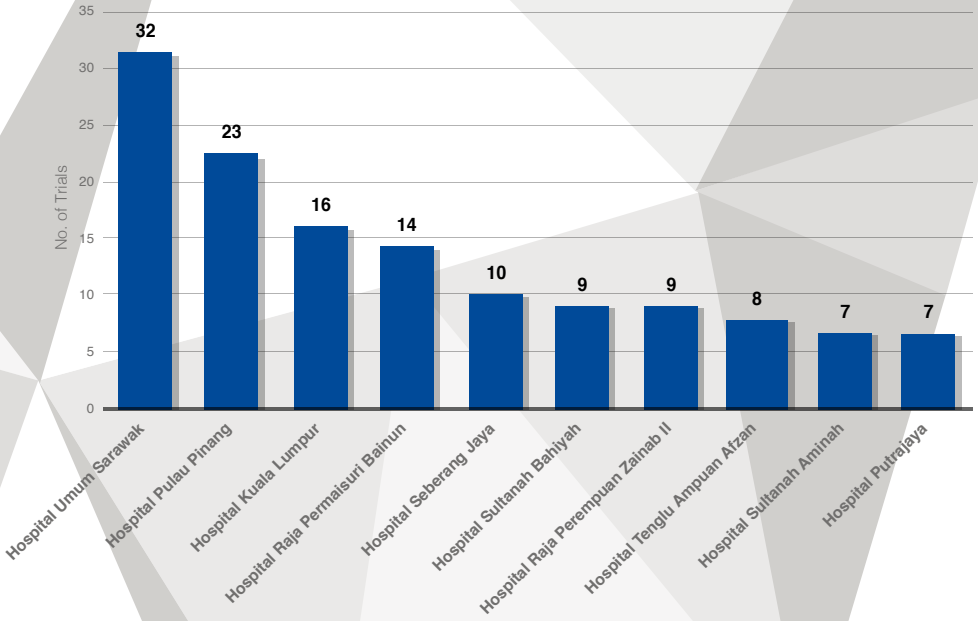




ISR trials in 2014 according to State

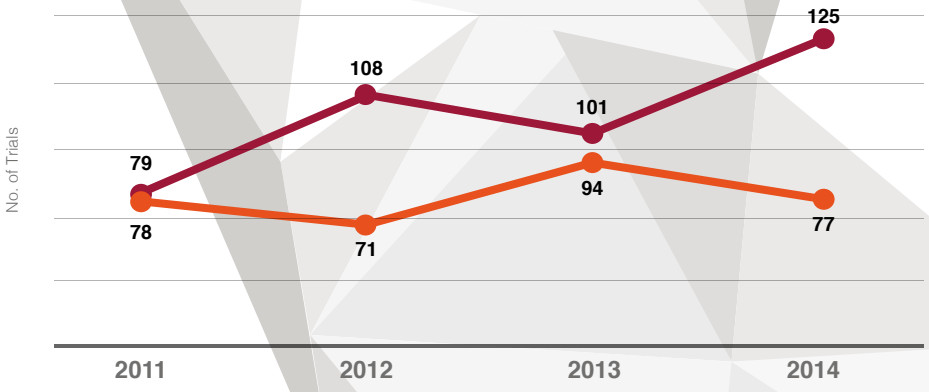
202 new ISR trials were approved in 2014 with a total of 421 individual sites. Federal Territory of Kuala Lumpur accounted for 120 sites, followed by Penang with 83 sites and Selangor with 50 sites.

Note:
The number represents total individual ISR at each state and there may be duplicates of the same ISR at other states, with different Principal Investigators.



Top 10 most active sites in 2014

Hospital Umum Sarawak was the most active with 32 trials, followed by Hospital Pulau Pinang (23 trials), and Hospital Kuala Lumpur (16 trials).

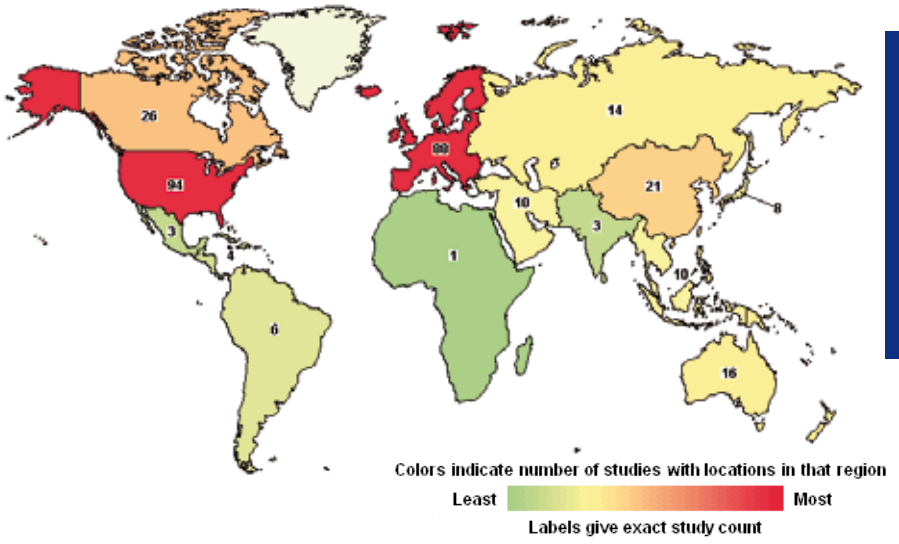


ISR Trials conducted at MOH and non-MOH sites

MOH sites conducted the bulk of ISR trials conducted in Malaysia. For 2014, MOH sites accounted for 125 new ISR trials while non-MOH sites (universities and private hospitals) accounted for 77 new ISR trials.

Neurology Statistics

Location of Industry-Sponsored Neurology Trials Worldwide (2010 – March 2015)



A total of 157 neurology-related ISR trials were conducted worldwide between 2010 and 2015. The United States recorded the highest number of trials (94), followed by Germany (46), the United Kingdom (35), France (34) and Spain (29).

Source: clinicaltrials.gov, March 2015

Number of ISR Neurology Trials in Southeast Asia (2010 – March 2015)

A total of 10 neurology-related ISR trials were conducted in Southeast Asia, of which the participating countries were Malaysia, the Philippines, Singapore and Thailand.

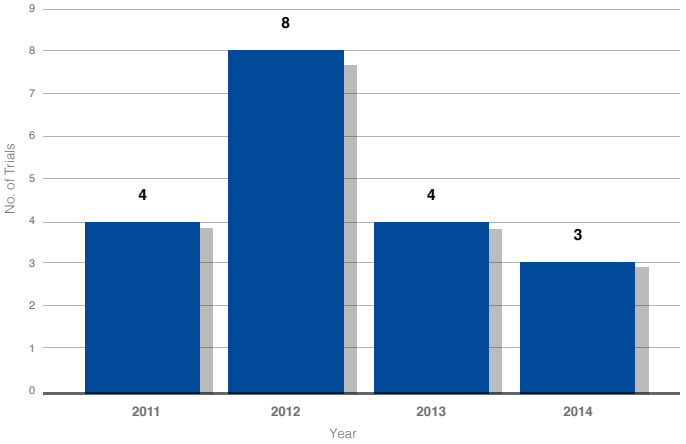
Note: The location and number of ISR Neurology trials worldwide and in Southeast Asia takes into account all studies (open and close) between 2010 and 2015. Neurology trials included in this list is only limited to Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, epilepsy, amyotrophic lateral sclerosis and other neurodegenerative diseases. Please note that this list is not exhaustive and only includes studies registered with clinicaltrials.gov.

Source: clinicaltrials.gov, March 2015

Location	Number of Studies
World	157
↳ South East Asia	10
• Malaysia	7
• Philippines	4
• Singapore	8
• Thailand	3

Note that some trials were conducted in multiple countries.

Studies with mulitple locations are included in each region containing locations.



ISR Neurology Trials Approved by IRBs in Malaysia

2012 saw the highest number of approvals granted by IRBs in Malaysia, while the lowest was in 2014 with only 3 trials.

**Note the difference in number of ISR neurology trials approved by Malaysian IRBs compared to the number of ISR neurology trials recorded in clinicaltrials.gov. The difference is attributed to the likelihood that some trials that had been approved by Malaysian IRBs were not registered in clinicaltrials.gov.*

Research Personality

Dr. Irene Looi

Consultant Neurologist, Seberang Jaya Hospital, Penang

Watch the interview on YouTube

Dr. Irene Looi is a Consultant Neurologist at the Medical Department of Seberang Jaya Hospital, Penang. She obtained an MBBS from the University of Malaya before pursuing MRCP (UK), Fellowship in Neurology and sub-specialty training in Stroke from the National Neuroscience Institute of Singapore. Prior to her current attachment at Seberang Jaya Hospital, Dr. Irene served as a Neurology Fellow at Penang Hospital, Kuala Lumpur Hospital and University Malaya Medical Centre between 2005 and 2008, and as a Clinical Neurologist at Penang Hospital (2008 – 2009).

Over the last several years, she has been a Principal Investigator in numerous multi-centre studies ranging from Parkinson's disease to Epilepsy. With almost a decade of experience under her belt, Dr. Irene has successfully published various research papers in national and international peer-reviewed journals.

Can you describe how you first got started in a clinical trial?

I started off as a Principal Investigator back in 2005 when I was still a neurology trainee at Hospital Pulau Pinang (HPP). An international CRO approached me to take up a Parkinson's disease clinical trial. While I was interested in this trial, I was worried and apprehensive at first, not knowing what to expect of a clinical trial. It was Dr. Ong Loke Meng's (Head of CRC at HPP) support and encouragement that gave me the caurage to venture into unchartered waters. HPP at that time had about 160 to 200 Parkinson's patients and the trial only requested for five subjects. That being said, I managed to recruit 10 subjects for my first clinical trial; giving me the confidence to boldly take up another two Parkinson's trials that very same year.

Did you have any role model or mentor who was instrumental in your journey as a Principal Investigator?

Most definitely. Dr. Ong Loke Meng is one of them. I have always admired his profound knowledge in clinical research. He is always generous in sharing his experience in this field, imparting valuable advice on ethical issues and supporting me and my research team in more ways than one.

My next role model is Professor Dr. Amir S. Khir (Dean of Penang Medical College (PMC)). It was when Prof Amir asked me to be a sub-Investigator in his clinical trial that I learnt how the CRC at PMC functioned. His research team was very organised and systematic. Prof Amir made sure that members of his team are compensated adequately for the time spent in managing a trial and I have taken it upon myself to continue this creditable move in every trial that I conduct.

Who do you feel plays an important part in a clinical trial?

I cannot emphasise enough the role of study nurses/study coordinators in a clinical trial. They act as commanders, from arranging for patients visits to managing specimens and completing the study documentation, to say the least. An experienced team of nurses and study coordinators makes all the difference in the conduct of a clinical trial. Personally, I feel that the nurses at the MOH hospitals are doing an excellent job in being very meticulous in their work.

What types of neurology trials have you conducted and what are your views on the advances made in neurology clinical research?

I have conducted about 6 – 8 Parkinson's disease trial, 2 – 3 epilepsy trials and a few dementia trials. Of late, research in neurodegenerative diseases and neurosciences are gaining momentum to find biomarkers that can diagnose disease long before neurological symptoms emerge, and to identify targets for drugs that might halt or slow neurodegeneration. Because of this, we are seeing a lot of new drugs coming into the clinical trial industry to treat these diseases.

What do you enjoy most about being an investigator?

Firstly, being able to provide new and potential drugs to my patients especially those who are in the advanced stages of Parkinson's disease. For some of these patients, I have tried all the available drugs in the market to control their disease. Yet there are some who still come to me and ask if there are other drugs which they can try. Since taking up clinical trials, I can now offer them these new drugs and it gives them hope for a better treatment.

Secondly, clinical trials helped develop a better rapport with my patients. During normal visits, I may only see my patients for 5 – 10 minutes, compared to 2 – 3 hours if they are in a trial. This makes them eager to participate in subsequent trials and thus makes patient recruitment easier.

Finally, by being involved in a trial, I enjoy better networking with my colleagues in other departments as well as with internationally renowned neurologists and neuroscientists.

Facilities at the Clinical Trial Unit, Seberang Jaya Hospital

A radiologist performing a CT scan

How has conducting trials affected your clinical practice?

It has changed the way I advise and counsel my patients on diseases like dementia. Before, my response to their queries on prognosis was that it is a neurodegenerative disease and it will progressively worsen, with no definitive cure. Now, I am able to tell them that although it is degenerative in nature, many clinical trials are currently underway and new potential drugs may be discovered in the near future. This gives them hope and optimism to deal with their disease.

How important is it for an investigational drug/product (that showed significant benefits to patients) to be continued even after a study closes?

Very important indeed. In normal scenarios, the trial drug will be stopped after a study closes. However, most sponsors will allow for compassionate use of the investigational drug until that drug is marketed in Malaysia. Should a Principal Investigator (PI) want the investigational drug to be continued for their patients after a study closes, the PI must ensure that this clause is included into the Clinical Trial Agreement before signing this all-important document.

Dr. Irene demonstrating a nerve conduction study on a patient

Do you recall any memorable patients from the clinical trials you have conducted?

I had a 60-year old patient who had been on two different anti-epileptic drugs which did not seem to be working on her. However, when she enrolled in an epilepsy trial, her seizures came under control. I managed to get the sponsor to continue that drug for this patient and they were more than willing to agree. She has been on this drug for the past three years and so far there has been no recurrence of seizures.

What kind of breakthroughs in neurology do you wish to see in the next 5 to 10 years?

It is my hope to see breakthroughs in new drugs and interventions for neurodegenerative diseases that can not only prolong life but most importantly improve the quality of life of these patients.

Clinical Trial Unit at Seberang Jaya Hospital

CRC Seberang Jaya has recently been accredited by NPCB (National Pharmaceutical Control Bureau) as a GCP–compliant bioavailability & bioequivalence site. How will this accreditation affect the conduct of clinical trials in CRC Seberang Jaya?

This accreditation encourages the CRC research team to be consistently GCP compliant, prioritize patient safety and ensure the quality of data storage. Thanks to this accreditation, we have also had offers from foreign sponsors to conduct bioavailability trials here.

What advice would you give to young clinicians who want to be involved in a clinical trial?

Clinical trials are the future to modern medicine and as clinicians, we have to embrace it, like it or not. CRC is always here to help those interested to take up clinical research. When I first got started, clinical trials seemed to be like a daunting task. Later, I found that it was nothing of that sort. Teamwork is the key to successfully conducting a clinical trial. So don't worry too much and just do it!

Dr. Irene Looi

TENGKU AMPUAN AFZAN HOSPITAL

Hospital Tengku Ampuan Afzan (HTAA) was built in 1904 and covers an area of 40.1 acres in the middle of Kuantan town. This Ministry of Health-owned medical facility was designed to provide affordable healthcare and to deliver high quality and efficient medical services to more than 600,000 residents of Kuantan and neighbouring areas. HTAA serves as a teaching hospital for the Faculty of Medicine of the International Islamic University, Malaysia. Its ambition is to become a center of excellence in healthcare through the spirit of professionalism, caring services and teamwork as advocated by the Ministry of Health Malaysia.

"Doctors at HTAA are very much committed to their clinical work as well as excelling in research. It is my hope that in five years, the Clinical Research Centre at HTAA will be on par with other established CRCs, equipped with adequate facilities and a proper dedicated CRC space for researchers to conduct clinical research in a conducive environment."

Dato' Dr. Marlia BT Mohammad Salleh
HTAA Hospital Director

The Clinical Research Centre at HTAA has been operational since November 2003 as part of the network of Clinical Research Centres (CRC) of the Ministry of Health. Its objectives include cultivating a research culture among clinicians, compilation of information regarding all clinical research activities in HTAA and providing assistance to researchers. CRC HTAA is headed by Dr. Selva Kumar a/l Sivapunniam.

192 *Dedicated Medical officers*

Therapeutic research focus:

- *Cardiology*
- *Endocrinology*
- *Gastroenterology*

Potential ISR Investigators

Dr. Selva Kumar a/l Sivapunniam (Paediatrician)
Dr. Aishah bt Ibrahim (Respiratory)
Dr. Chan Chee Eng (Internal Medicine)
Dr. Peter Ch'ng Wee Beng (Dermatology)
Dr. V.A. Jacob a/l Abraham (Orthopaedician)
Dr. Gowri Sundaram (Respiratory)
Dr. Zainal Abidin (Accident & Emergency)
Dr. Ahmad Zafri b. Abu Bakar (Psychiatrist)
Dr. Siti Khairani bt Zainal Abidin (Cardiologist)

793 *Beds*

Active Principal Investigators

Dr. Tee Hoi Poh (Gastroenterology)
8 trials: Hepatitis B (4) and C (1); Ulcerative Colitis (1); CA stomach (1); Hepatocellular carcinoma (1)

Dr. Abdul Hadi b Jaafar (Cardiology)
3 trials: Atherosclerosis (1); Cardiovasuclar (1); Observational study (1)

Prof Dr. How Soon Hin (Respiratory)
2 trials: CA lung (2)

Asst. Prof Dr. Nik Nur Fatnoon bt Nik Ahmad (Internal Medicine)
6 trials: Type 2 diabetes mellitus (6)

Dr. Anwar Irawan b. Ruhani (Cardiology)
1 trial: Cardiovascular outcome in type 2 diabetes mellitus (1)

Dr. Che Rosle Draman (Nephrology)
1 trial: Lupus Nephritis (1)

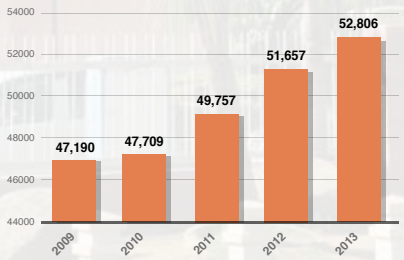
Dr. Hilmi Abdullah (Internal Medicine)
1 trial: Rheumatoid arthritis (1)

Dr. Harris Ngow Abdullah Cardiology)
1 trial: Cardiology (1)

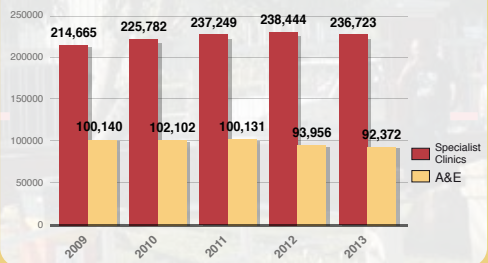
40 *Wards*

123 *Skilled Specialists*

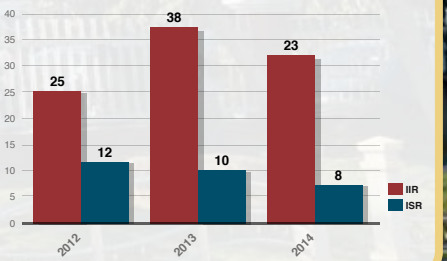
Inpatient visits between 2009 - 2013



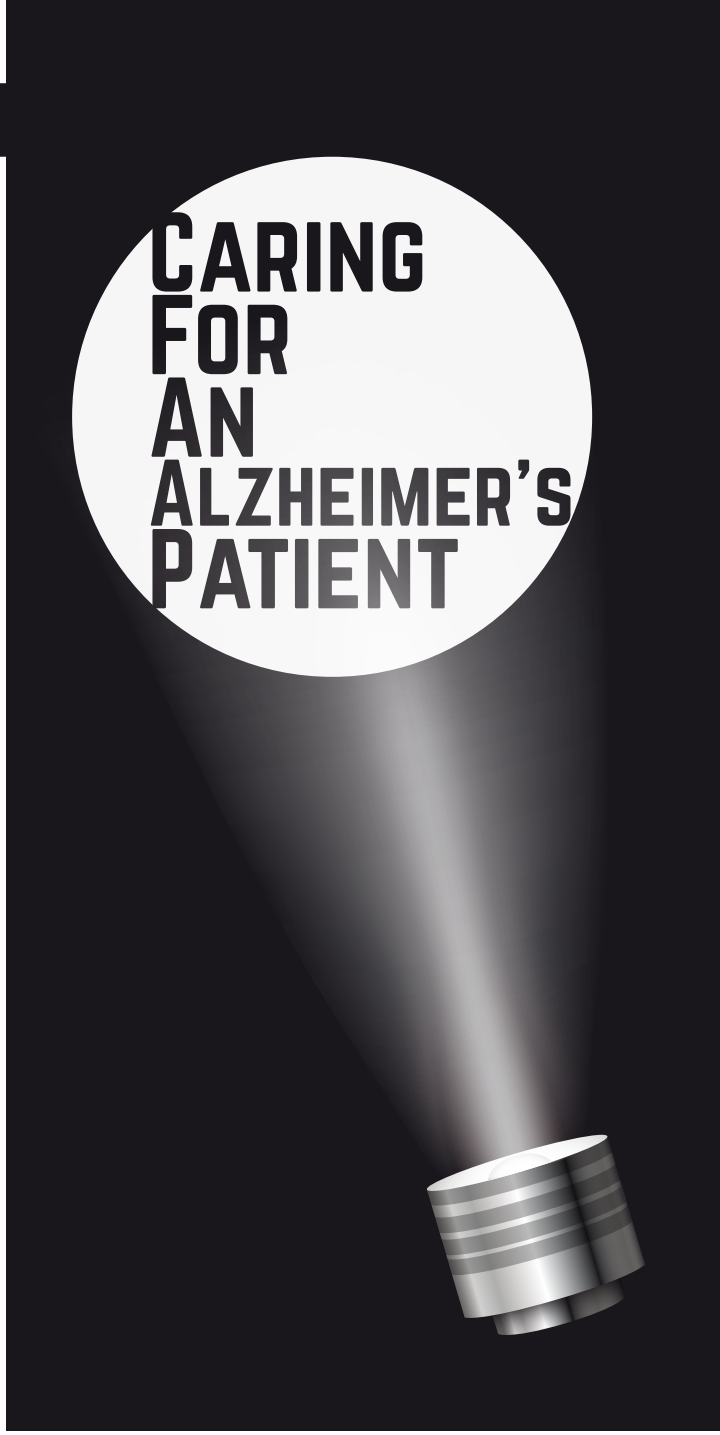
Specialist clinics and A&E visits between 2009 - 2013



Total number of trials at HTAA



Caring For An Alzheimer's Patient



When Sharmila Valli Narayanan's mother was diagnosed with Alzheimer's in 2005, no one in her extended family had heard of the disease. She tells what it is like seeing a loved one suffer from the disease. Despite the pain, there are also lessons to be learned about love, sacrifice and courage.

• • •

My mother was diagnosed with Alzheimer's in 2005. My father and I were sitting in the doctor's room when the doctor told us that my mom's brain had atrophied over the years. She said this based on the two CT scans that she checked. One was taken in 1999 when mom had a major stroke and the other was taken recently. Based on the scans and some tests that were conducted earlier, she concluded,"No doubt about it. Your mother has Alzheimer's. I would say she is now in the moderate stage of the disease." With these few words, the doctor changed the course of our lives forever.

My father and I looked at each other and blinked. Alzheimer's? That was a disease we normally associated with Americans thanks to the most famous patient with Alzheimer's at that time – former President Ronald Reagan – who had passed away from that disease in 2004. No one in our family had that disease and we did not know of anyone at all who suffered from it.

Alzheimer's Disease is the most common form of dementia. It is not a normal part of aging but a disease involving the progressive loss of brain nerve cells. In my mom's case her Alzheimer's was precipitated by her stroke in 1999. The stroke changed her personality. Her short term memory was badly affected and she became more quiet and withdrawn. But she still was the same loving mom who took care of the household. No doubt she kept forgetting her old recipes and wasn't spontaneous in her conversation but some how she went on with her life.

The first time we realised that mom was acting "strange" was when she accussed some relatives of stealing her things. For example, once she was convinced that her youngest sister had stolen her bottle of perfume. But later the perfume turned up in my mom's bag. My sisters and I turned to Google to find out why mom was acting like she did. That's when we first came across symptoms of Alzheimer's. I was still in denial that mom might be suffering from the disease. Then something happened that jolted me out of my stupor. One night in 2005, my mother called me and said in an agitated voice that my father was trying to kill her. I was shocked beyond words and knew that something was terribly wrong with her for her to think this of my kind and loving father. It was this and some other erratic behaviour of hers, which caused my family considerable pain and embarrassment that finally brought us to the doctor's office.

Sharmila Valli Narayanan

The doctor looking at the stunned expression on my face explained to me gently that there is no cure for Alzheimer's. "It gets worse over time. The medicine we prescribe can only delay the worst effects, not cure it," she said.

I remember coming home and telling mom about the disease that she had and what it would eventually do to her. She listened impassively. Later she announced she was making dinner. When I told her that we could go out for dinner mom said with a gentle voice, "Let me cook for my family as long as I have my memory because one day I know I will not be able to do it."

Alzheimer's affects people differently. My mom eight years after her diagnosis, performed as a "high functioning" Alzheimer's patient. I think one reason for this is because from the moment she was diagnosed, the doctor at Hospital Sultan Ismail, Johor Bahru, put her on rivastigmine. Rivastigmine does not cure Alzheimer's; it helps to slow down the deterioration of the disease. My mom can cook, look after herself and still remembers who we are. Some relatives who have not seen her for some time often remark how "normal" she looks and behaves. Some have even asked whether mom really has Alzheimer's.

But those of us who are with her very often know that the disease has taken a toll on her. Her short term memory has become worst and in the last two years her deterioration has been quite marked. She no longer knows how to use the telephone or the remote for the TV. Learning new tasks are impossible for her.

In 2013 a few days before her 75th birthday, her condition suddenly deteriorated further. She stopped eating food and would only take liquids. She, who, despite her Alzheimer's, took great care in her personal appearance and hygiene, could not control her bowel movements and had to resort to wearing adult diapers. She had to be bathed and fed. All this was too much for my 77 year-old father to handle alone.

I had come down to visit her a few days after her birthday and was shocked at the changes. I made a decision to move down to my hometown from Kuala Lumpur to help care for my mom with my dad for as long as I could.

Carers for Alzheimer's will often find themselves taking on the role of parent to their parent. So it was with me. Mom has her good days when she would eat, go for walks and be very responsive. She also has bad days when she would throw tantrums with her food like an annoying toddler, withdraw into her shell and seem unreachable. I learned to focus on and celebrate her good days.

Her slow decline has also made me come to terms that she will not be around for long. So I cherish each day with her and make sure I tell her that I love her. Her illness has also brought out the best in my father. My dad is a very traditional Asian man who expected his wife to serve him and look after him. But now the roles have been reserved. He looks after her very well and with devotion. Looking at him tending to her needs, I realised this is true love – to be there for your partner, whether in sickness or in health but especially in sickness.

Somehow my mom rebounded from that downward spiral in 2013. We had taken her to a neurosurgeon who specialised in geriatrics and after some blood tests, she added some new medications. Now my mother is able to look after herself and if she is in the mood, she actually goes into the kitchen to cook.

If you have a parent or a loved one who has been acting strangely, here's my advice: get them tested with a geriatric specialist ASAP. The patient will say he or she is ok, but do it anyway. If a patient is diagnosed in the early stages of Alzheimer's, drugs like rivastigmine can help to slow down deterioration and allow them to be independent and be themselves for longer periods.

Reach out to support groups like Alzheimer's Disease Foundation Malaysia (ADFM), www.adfm.org.my, for help with information and other resources.

Dispelling the Myths Surrounding Alzheimer's Disease

Myth 1: Only older people can get Alzheimer's

Most people with Alzheimer's are 65 and older. But it can happen when you're younger, too. About 5% of people with the disease get symptoms in their 30s, 40s or 50s. It's called early-onset Alzheimer's.

Myth 2: Memory loss is a natural part of aging

Some memory loss is a normal part of aging. But Alzheimer's symptoms, like forgetfulness that interferes with your daily life, and disorientation, are not. Its normal to forget where your keys are from time to time. But forgetting how to drive to a place you've been many times, or losing track of what season it is, points to a more serious problem. As the disease gradually worsens, it takes away someone's ability to think, eat, talk and more.

Myth 3: Medications can stop Alzheimer's disease

The Food and Drug Administration (FDA) has approved several medications that may help slow the progression of Alzheimer's disease – but these are not considered cures.

Research Personality

Dr. Suraya Yusoff

Psychogeriatricians, Hospital Sultan Ismail, Johor Bahru

Running a Clinical Trial for an Alzheimer's Drug

Dr. Suraya Yusoff is a psychogeriatrician -- a psychiatrist who specialises in the assessment and treatment of elderly people with mental health issues. She is one of the few psychogeriatricians in Malaysia. Currently she is based at the Hospital Sultan Ismail in Johor Bahru, where she runs a clinical trial for a drug to treat Alzheimer's. She talks to **Sharmila Valli Narayanan** about the challenges of running a clinical trial for Alzheimer's patients and explains the importance of such trials for patient care.

Dr. Suraya Yusoff is soft spoken and calm – two qualities very much needed when dealing with patients with psychiatric problems. She specialises in psychogeriatrics, a branch of psychiatry that deals with the study, prevention and treatment of mental disorders in elderly people.

As a medical student, she had been attracted to psychiatry, but her parents discouraged her from pursuing it. "There was and still is a stigma attached to psychiatry. People think it deals with people who have gone mad. My parents wanted me to try something else," says Dr. Suraya. Consequently, she started off her career in paediatrics but circumstances were such that she ended up specializing in psychiatry anyway. Dr. Suraya was attracted to psychiatry because she saw it as providing more holistic treatment for patients.

"I felt that in other fields of medicine you treated the physical aspect of the patient, sometimes without looking into personhood, while in psychiatry you have to establish a relationship even before you can start treating the patient. So it is not just a matter of looking at the physical symptoms but needing to balance the patient's emotional needs as well. I liked this personal relationship aspect of psychiatry."

Dr. Suraya, who graduated from University Malaya in 1984, went into psychogeriatrics thanks to a meeting with a visiting psychogeriatrician from the United Kingdom when Dr. Suraya was doing her postgraduate studies in Universiti Kebangsaan Malaysia. This was in the early 1990s and psychogeriatry was a relatively new field in the United Kingdom as well. Psychogeriatry was introduced in the United States (where it is known as geropsychiatric or geriatric psychiatry) in 1984. With an aging baby boomer population, the doctors in the West realised this segment of the population had special psychiatric needs that were not being meet.

What especially attracted Dr. Suraya to this new field was the large amount of community work involved. “You were not stuck in the hospital all the time. In places like the United Kingdom, the doctors do a lot of work with the community where they visit patients’ homes,” she says. “Plus, I enjoy working with elderly people – generally they are a very nice group of people to work with.”

Dr. Suraya did her sub specialization in psychogeriatry in the United Kingdom right after she completed her gazettement as a MOH psychiatrist in late 1994. She returned to Malaysia in 1996 as the first psychogeriatrician in the country and was posted to Hospital Sultanah Aminah in Johor Bahru where she set up a psychogeriatic unit in 1998. The unit was later moved to Hospital Sultan Ismail (HSI) when she was transferred there.

At present, Dr. Suraya also trains other doctors in this field and has the distinction of being the only psychogeriatric in the country who oversees a community psychogeriatric service. “I have two nurses under me and we cover an area of about 40km,” explains Dr. Suraya. “We see patients who have severe dementia, behavioural problems, are not mobile and therefore not able to come to the clinic at HSI. As a psychogeriatrist I don’t just focus on the treatment but also act as a physician to these patients because most often they also have other physical illnesses such as diabetes, high blood pressure, to name a few.”

Running a clinical trial for Alzheimer’s

Dr. Suraya is also involved in running a Phase 3 clinical trial on an anti-dementia drug specifically for Alzheimer’s patients. She explained about the meaning of the different phases a new drug goes through before it reaches the public.

This particular clinical trial is a 15 month study of patients with mild to moderate Alzheimer’s disease. It is a multicentre study which involves the US, Europe, Asia and Australia. Malaysia is one of the two countries chosen from Southeast Asia. The trial started at the end of 2013 when the doctors involved were given a year to recruit patients for the study. The trial will end in mid 2015.

Challenges faced

Two phases of the trial will be run. The first (which is ongoing) is a double blind study, informed Dr. Suraya. “In a double blind trial, the doctors and the patient don’t know whether the drug used is the actual drug or a placebo. In the open label trial the doctors will know whether the patient is being given the drug or the placebo.”

Only three centres in Malaysia are being used in this clinical trial: HSI in Johor, UniKL Royal College of Medicine Perak and University Malaya Medical Centre (UMMC). The target was to recruit 10 patients for each centre. Unfortunately, meeting this target has been tough. “For HSI we selected 16 patients for the trial, but in the end only 5 were deemed fit for the study; in Ipoh 19 were screened but only 9 were finally selected for the trial and in UMMC, out of the 5 patients who were selected only 1 made it into the trial. So instead of having 30 patients for the trial, we only managed to get 15 patients – that’s barely more than half,” discloses Dr. Suraya.

Dr. Suraya listed several reasons why it has been difficult to recruit patients for this clinical trial . “Most Malaysians are not used to being a part of a clinical trial and they are not sure of what to expect. With Alzheimer’s patients there are additional challenges inrecruiting them for clinical trials.

Most of them can't make decisions on their own because of their impaired cognition which makes it difficult for them to give consent. The decision has to be made by their primary caregiver which could be one of their children. But in Asian families, the decision is not made by the main caregiver alone; often times the whole family will be involved in the decision making and this can take time and become complicated."

"Some patient who are already on an anti-dementia drug are very reluctant to try a new drug especially one that is being tested on patients," continues Dr. Suraya. "They don't want to be a guinea pig.

Communication between doctor and patients is essential during the clinical trial period. With Alzheimer's patients, most often it is the caregiver who has to communicate to the doctor on how the patient is feeling and whether they are experiencing any side effects because the patients themselves are unable to do so. "On my side the problem I face is that the doctors under me tend to move around to other departments and I am not able to have the same set of doctors and nurses to monitor and rate the patient", notes Dr. Suraya.

Despite the challenges, the trial has been progressing well and Dr. Suraya is looking forward to when the trial enters the open label phase. According to The Alzheimer's Society, the disease affects about 36 million people around the world. Many countries in Asia, with an increasing ageing population can expect more people to develop the disease in future.

Dr. Suraya hopes that there will be more such clinical trials for Alzheimer's in the future and that Malaysia will be included in the list of countries where the trials will be carried out. "Such trials for Alzheimer's drugs are very important because we need to advance the care and treatment for this devastating disease. Right now there are only about three types of drugs used for treating patients and we need to find more. This disease might affect us and I hope that should I get it 30 or 40 years from now I hope to God that there are more effective drugs available for treatment. The only way we can get such drugs is to learn their efficacy via clinical trials. I sincerely hope that in future if there are more such trials, my colleagues in the medical fraternity will be more willing to be involved in the trials."

She also has advice for Malaysians who are approached to take part in clinical trials.

"I fervently hope that Malaysians are more daring to come forward and be part of clinical trials. Malaysians are generally afraid of the unknown. I would like to assure them that being part of a clinical trial is the safest place to be because the patient is given excellent care during the clinical trial. At this stage, the drug has undergone a lot of tests and is safe for humans. Doctors monitor the patient every few months and look out for any side effects, so there is really nothing to worry about," sums up Dr. Suraya.

FAQ:
How does the GST (Goods & Services Tax) Relate to Clinical Trials in Malaysia

Feedback from ROYAL MALAYSIAN CUSTOMS DEPARTMENT

Can the clinical research industry or sponsors & Contract Research Organization (CROs) be considered for zero-rating or exemption from the GST, in view that:

- **ISR can be considered as FDI.**
- **ISR is helping to develop R&D capability in Malaysia.**
- **Malaysian patients are benefitting.**

Customs Department maintains its stand that there is no zero-rating or exemption from GST for the Clinical Research industry or sponsors & CROs.

Should sponsors & CROs submit for GST return on a monthly or quarterly basis?

The default is quarterly basis. If the annual turnover is more than RM5 million, then the sponsors & CROs are allowed to submit monthly. If the annual turnover is less than RM5 million, then they would have to submit quarterly. However, they have the option of requesting to the DG Customs if they want to submit on a monthly basis.

Note: A company or entity has to be registered mandatorily under GST if annual turnover exceeds RM500,000.

For work completed before 1st April 2015, but payment is made or received after 1st April 2015.

a) **Is the payment subject to GST?**

No, the payment is not subject to GST if the work was completed before 1st April 2015. Please refer to S.183(1) GST Act 2014.

b) **Should the invoice be backdated to before 1st April 2015?**

The invoice can be issued as usual, no back-dating required. But need to attach supporting documents to show that the work was completed before 1st April 2015.

A local company (CRO/sponsor) signed the contract (eg. Clinical Trial Agreement - CTA), but request for invoices to be addressed to a foreign party (eg. the CRO's Asia Pacific Regional Office).

a) **Is GST chargeable in the invoice?**

Under GST, the services performed in Malaysia will be subjected to GST. The tax invoice must be issued with GST by the service provider to the recipient. If the recipient is registered under GST, the recipient can claim input tax claim. If tax invoice is billed to the global or regional office (overseas), input tax cannot be claimed by the global/regional office since they are not GST-registered. GST can only be claimed back if the invoice is addressed to a local address/entity (provided they are GST registered).

b) **Should invoices addressed to foreign parties be amended to show a local company or address?**

If they want to claim back the GST paid, then they need to use a local company or address that is GST-registered with Customs.

For clinical trials conducted in Malaysia, if the CRO or sponsor wants to claim back any GST paid to Customs, then will need to ensure that the invoice is addressed to a local company/address that is GST-registered with Customs. Otherwise, they will not be able to claim back the GST.

Assuming the CTA has been signed by a foreign sponsor/CRO, will CRM charge GST to the overseas sponsor/CRO?

CRM will not charge GST to overseas sponsors/CROs, as export services are not subject to GST. (Note: Under current guidelines, it is a requirement that the CTA be signed by signatories based in Malaysia).

For agreements/contracts that have been signed previously, but not completed before 31st March 2015, will it now be subjected to GST?

a) GST will be charged on the balance value or scope of work that is not completed as at 31st March 2015.

b) Agreements/contracts will need to be reviewed/amended to reflect imposition of GST on the balance value or scope of work that remains to be done after 31st March 2015.

CRM is studying possible methods to fulfil the legal requirements but without the need to amend existing CTAs. One option is to affix an Addendum to the existing CTAs.

For invoices issued by CRM, which items will be subjected to GST?

a) The 15% management fee (of the value of the trial budget) paid to CRM is subject to GST.

b) Monies that are due to the P.I or service providers is not subject to GST in the invoices issued by CRM, because that portion or amount is not an income or revenue of CRM but instead received on behalf of the PI/service provider and will be paid to the PI/service provider.

Should the Principal Investigator charge GST to the CRO or sponsor?

a) If the P.I makes extra income (excluding monthly salary) exceeding RM500,000 from doing clinical trials and/or other sources (but not including monthly salary),

then the P.I has to register with Customs and must charge GST to CROs/sponsors.

b) If the P.I's extra income (from all sources but excluding monthly salary) is less than RM500,000, the P.I does not need to register with Customs for GST.

c) P.I's that charge CROs/sponsors for GST will have to pay the GST to Customs. They can later claim back the GST by submitting monthly or quarterly returns to Customs. (refer to Q.2)

Based on CRM's records, no P.I currently makes RM500,000 or more annually from doing clinical trials.

P.I's that do make extra income exceeding RM500,000 (from whatever sources but excluding monthly salary), a mandatorily required to register with Customs for GST.

How will GST affect the clinical trial budget?

a) Some costs will increase due to the chain effects of GST. However if the CRO/ sponsor are registered under GST with Customs, the input GST can be claimed back.

b) Outsourced services such as MRI, CT scan, lab test, archiving services, etc. will be subject to GST if the vendor is not registered with MOH as a private healthcare facility under the PHFSA 1998 and is GST-registered with Customs.

Private healthcare facility registered under the PHFSA 1998 cannot charge "output GST" and cannot claim "input GST" from Customs.

How will the GST be reflected in the CTA?

Parties to the CTA will have to differentiate between private healthcare facilities registered or licensed with MOH which are exempted from GST under Paragraph 18, GST, and out-sourced facilities and services other than the above, and also consider if the PI is registered or not with Customs.

Can a CRO claim input GST from local vendors/sites?

If the CROs are GST-registered, and a tax invoice with 6% GST is charged, the input GST can be claimed back from the Customs Dept.

Is GST applicable for private hospitals?

GST is applicable to private hospitals but private hospitals cannot claim back from Customs.

Private healthcare facility registered under the PHFSA 1998 cannot charge "output GST" and cannot claim "input GST" from Customs.

Is GST applicable for private labs providing CT scan services?

Yes, GST is applicable for private labs provided the private lab is registered with the Customs Department.

GST is applied to outsourced services such as CT scan services and lab services if the vendor is not registered with MOH as a private healthcare facility under the PHFSA 1998 and is GST-registered with Customs.

If the SC's fees belong to CRM within the study budget, (regardless if the PI is GST registered or not), will CRM charge the 6% GST for the SC fees to the PI?

Yes, CRM will charge the sponsor 6% GST for its SC fees as CRM is a GST-registered company.

Currently, majority of sites do not generate "tax invoice" for PI/site payment and payment is generated based on CRA's tracker. Upon GST implementation, local sponsor can only make payment with tax invoices.

(a) For payment to CRM, can there be a standard "tax invoice" generated for study payment?

Yes, CRM can issue the tax invoice if the study budget is managed by CRM. If the PI's income (excluding monthly salary) exceeds RM500,000, another tax invoice from the PI will be required.

(b) For payment to Societies (if the study budget is managed by them), can the Society generate "tax invoice"? If not, can the PI or hospital issue a tax invoice?

Depends on each individual society, whether they are GST-registered.

CROs/sponsors are requested to seek clarification from any Society that is managing their trial budgets.

How long will the refund of GST take?

Refund of GST from the Customs Department will take 14 days, if the Input GST is more than Output GST. Otherwise the Input GST can be "set off" against the Output GST.

Payment is tracked at study site level and made by sponsor to CRM via cheque with supporting documentation/tracker on the payment breakdown. How will the tax invoice be issued? Does it breakdown the items or split between non-GST and GST? Will tax invoice be issued before a payment is made to CRM or after the payment?

The tax invoice from CRM will state which items are subject to GST. Whether the CRM tax invoice is issued before or after payment depend on what the CRO/sponsor wants. Some may ask CRM to issue an invoice before payment, while some will pay first and then request CRM to issue the tax invoice.

What will be the expected turn-around time for CRM to issue a tax invoice?

It will take between 1 to 3 days.

Note:
CROs – Contract Research Organizations
CTA – Clinical Trial Agreement
PI – Principal Investigator/Doctors

SCIENTIST TO WATCH

Dr. Swee Tan

ONZM MBBS PhD FRACS

Founder and Executive Director of the Gillies McIndoe Research Institute, Wellington, New Zealand.

Consultant Plastic & Cranio-Maxillofacial Surgeon at Wellington Regional Plastic, Maxillofacial & Burns Unit, Hutt Hospital, Wellington, New Zealand.

Dr. Swee Tan is the Founder and Executive Director of the Gillies McIndoe Research Institute and a Consultant Plastic & Cranio-Maxillofacial Surgeon at the Wellington Regional Plastic, Maxillofacial & Burns Unit, Hutt Hospital, Wellington, New Zealand. He obtained an MBBS from the University of Melbourne in 1985 and an FRACS from the Royal Australasian College of Surgeons in 1992. Sparked by his interest and passion in researching the cause of, and a better way to treat strawberry birthmarks, he enrolled for a part-time PhD degree at the University of Otago and graduated in 2001.

He was appointed the Director of the Wellington Regional Plastic, Maxillofacial & Burns Unit, Hutt Hospital between 2000 and 2006 and Director of Surgery at the Hutt Valley District Health Board, Wellington, a post he held from 2007 to 2013.

He is an elected member of 13 national and international professional and scientific societies and the past President of the Australian and New Zealand Head & Neck Cancer Society. Dr. Tan is internationally renowned for his research into vascular birthmarks and head and neck cancer. His team and their collaborators have received countless international award for their work.

The accolades he has received include the Officer of the New Zealand Order of Merit (ONZM), Wellingtonian of the Year – Science & Technology, 'Living Treasure' of the Museum of Wellington – City and Sea, the New Zealand Medical Association Chair's Award, the Royal Australasian College of Surgeons' Research Award, the Fervent Global Love of Lives Medal and the Inspire Welling Ambassador Award. Dr. Tan has authored over 110 publications in peer-reviewed journals and book chapters and has delivered numerous lectures at international conferences.

In the last National Conference for Clinical Research held at Kuching, Sarawak, CRM was privileged to meet and interview the good doctor who has made several medical breakthroughs, notably in the understanding and treatment of strawberry birthmarks.

A 3-month old baby with a large haemangioma involving the right cheek and eye socket pushing the eye upwards before (left) and 5 months after (right) low-dose propranolol treatment.

Dr. Tan, how did you first get involved in basic research?

My journey in basic science research began when I was on a craniofacial research fellowship at the Boston Children's Hospital and Harvard Medical School in 1995 following the realization that if I want to come up with a better treatment, I need to understand the cellular and molecular mechanisms that regulate the particular condition – and the one condition that interested me most was strawberry birthmark (a.k.a. hemangioma). Although a benign tumor, it is fascinating that hemangiomas have a built-in mechanism for proliferation and a system to self-destruct. Deep inside, I felt that if we got this figured out, then we would understand cancer better and maybe find a cure. And that's how it all got started.

What propelled you into this journey – the discovery of the origin and treatment of haemangiomas?

This was born out from my dissatisfaction on the existing treatment for hemangiomas. Many different treatments that had been developed over the last 100 years such as surgery, radiotherapy, steroids, interferons, chemotherapy and lasers – none was satisfactory. Having worked with children, I was all too familiar with their loss of confidence due to the disfigurement caused by hemangiomas, some of which also threaten function or life itself. As a new consultant in 1996, the strategy was to do nothing unless the condition warranted intervention.

Hemangiomas grow for up to a year and then gradually shrink. Some will disappear completely but about half of them will leave behind a blemish. The old paradigm was to do nothing, and if something had to be done, it would be aimed at stopping the growth and wait for nature to take its course. It might take between 5 and 10 years for the tumor to gradually regress. For those patients who were left with a blemish, surgery and/or laser was done, usually before the child started schooling. One of my first patients was a 6-year old girl whom I performed surgery on, in 1996, to remove a large fatty lump that distorted her upper lip and cheek, caused by a large hemangioma that had regressed. She and her family were delighted with the results but I was profoundly unhappy because her mother showed me a series of photographs showing the lesion growing from nothing to a large tumor before gradually shrinking, leaving her with a fatty lump. I was convinced that the only way to come up with a better treatment was to understand the biology of this tumor. To do this, I retrained as a scientist and enrolled as a part-time PhD student.

Are you still involve in clinical practice?

I probably work about 80 hours a week, one third spent on clinical work and the rest on research. I still very much enjoy clinical surgery and most of my work is head and neck cancer, followed by vascular anomalies.

How big is your research team at the Gillies McIndoe Research Institute (GMRI)?

The GMRI currently hosts 11 research staff and two research students. The two research students, one a 5th year medical student and the other a 4th year medical student who had elected to stay on at the GMRI after their summer placement to do a year of full-time research working towards a BMedSc (Hons) degree, before going back to complete their medical degree.

Where do you get your motivation to conduct research on haemangiomas?

The fact that the treatment we had back then was unsatisfactory and the desire to relieve the pain and trauma that these children had to go through spurred me on to come up with a simple and more effective treatment with less side effects. I believe that your success will be judged when you stop doing what you're doing now. Treatment for many types of head and neck cancer often involves surgery followed by radiotherapy and sometimes chemotherapy as well. Surgery is mutilating and some patients require hospitalization for a couple of weeks, followed by radiotherapy. Despite the radical treatment the chance of survival is about 50% and the statistics have not changed for 40 years. My hope is that one day, we will come up with a radically different treatment for cancer that bypasses everything that we have used in the last 100 years.

Dr. Tan, you have led your research team on the ground-breaking discovery that strawberry birthmarks are caused by stem cells regulated by a hormone system. Can you tell me more about this medical breakthrough?

When we discovered the stem cell origin of hemangioma we observed the expression of angiotensin converting enzyme, a component of the renin-angiotensin system, by these very primitive cells. We also observed that female, white and premature infants who have a high incidence of hemangioma also have high levels of renin, another component of the renin-angiotensin system. As we were piecing the pieces of the jigsaw puzzle together, we stumbled on case reports from two independent French groups, one using propranolol (a non-selective beta-blocker) and the other, acebutalol (a predominantly β1-adrenoreceptor blocker) respectively to treat the complication (cardiac failure) resulting from high-dose steroid treatment for hemangioma. Serendipitously the haemangiomas regressed dramatically. We put a list of all the known beta-blockers together and looked at their actions, and concluded that the common mechanism of beta-blockers was the effect on the renin-angiotensin system. Suddenly the whole picture emerged.

Research requires persistence, formulating a good hypothesis based on a concept and a bit of serendipity. It is when all the pieces of the puzzle are put together and something happens at the right time and at the right place that discoveries are made. This is why I feel that having a multidisciplinary input is important because you get to network with people with different backgrounds, unique expertise and perspectives.

Our discoveries underscore the new treatment of hemangioma based on modulation of the renin-angiotensin system that leads to dramatic shrinkage of these tumors within days, negating the need for the traditional treatment using high dose steroids, and lengthy and complicated surgeries over several years. Propranolol is now the treatment of choice for hemangiomas.

In your opinion, what are Malaysia's strength in terms of conducting clinical research?

Malaysia has the large patient pool that allows clinical trials to be readily conducted here as opposed to elsewhere like New Zealand which only has a population of 4.5 million. And there are a lot of capable clinicians and researchers as well as pharmaceutical companies that are interested in conducting trials in Malaysia. I think what needs to be improved is to make it easier for people who are interested to be involved to participate in clinical trials.

What are your thoughts on encouraging research among clinicians?

You want to encourage clinicians who are genuinely interested in answering a research question, motivated by their curiosity and wanting to push the boundaries. These are the people you want to encourage and assist. I don't believe in forcing people to get involved when their hearts are not in it.

Efforts should also be made in providing opportunities to the future generation to be involved in research. In New Zealand, opportunities are given to medical students between their first and fifth year of study to get involved in research. In the long run, we foresee that those who may have found interest in research may one day return as academic clinicians. We will end up with a pool of very talented and motivated researchers who are leaders in the country.

Where do you see yourself 10 years from now?

We have been taught that cancer is a problem of normal cells turning "bad" and this "bad" cell made multiple identical copies of itself that form the cancer. There is gathering evidence supporting our concept of cancer stem cells being the basis of cancer. These cancer stem cells are like the "queen bees" that give rise to the cancer cells (the "worker bees") which consist the bulk of the cancer. These worker bees do not multiply and have a limited life-span. The "queen bees" can make copies of themselves and they can travel to make other hives (metastases). They resist chemotherapy and radiotherapy by going into slow-cycle state which explains why cancers that had seemingly disappeared but only to return later. If this concept is correct, then the mechanism controlling these very primitive stem cells would be entirely different from those that control the cancer cells. While it's still a concept waiting to be proven, our treatment for hemangioma that targets the stem cells which is regulated by the renin-angiotensin system has shown promising outcomes.

So, ten years from now, I would like to think that we would come up with a new prototype for cancer treatment that does away with conventional cancer treatments that we have been using for the past century.

What would be your advice to young Malaysian researchers who wants to embark on the research journey?

For young researcher who are aspiring to be involved in the rewarding journey of research, they should obtain the necessary training and probably enroll in a higher degree. Having the training that goes with a higher degree definitely gives you a different perspective of looking at a particular problem, accessing it critically and developing a plan to address the research questions.

Dr. Swee Tan's Early Years

Dr. Tan rose from a poor family of 14 children on the outskirts of a tiny Malaysian village, Senggarang. His father had only primary school education, his mother none. They sent him to a Chinese school and after school he helped out in the plantations, weeding and collecting coconuts and coffee. It was clear from an early age that he didn't want to work that way forever. By the age of 9 or 10, he knew he wanted to be a doctor. Though people scoffed at the unlikely ambition of a young lad with calloused hands, he was more determined than ever.

He aspired to get into medicine in a Western country, but having a poor grasp of English, he attended Taylor's College in Kuala Lumpur for nine months to gain the Victorian High School Certificate. Over three terms, he learnt English by reading the newspaper daily, from cover to cover. He then worked in a bookshop in Singapore for a year to save. Australia was offering free tuition to a limited number of students from developing countries in the 1980s, and having gained a place, Dr. Tan began his studies at the medical school of the University of Melbourne. Three times a week, he got up at 5 o'clock in the morning to clean supermarket floors. In his final year, he was apprehended by a surgical registrar for being half an hour late to tutorials. Being given the chance to explain himself, the registrar offered to be a guarantor for his study loan.

Dr. Tan met and fell in love with Sanchia, a student nurse at Royal Melbourne Hospital, and graduated in 1985. In his fifth year, he did his elective in New Zealand and was enthralled by the beauty of the country and its people who were friendly, accepting, unpretentious, and happily "color-blind". Life slowly unfolded as he persevered in his quest to be a plastic surgeon and researcher.

To date, Dr. Tan has trained with some of the world's top plastic surgeons in Oxford and Boston. Challenged by the lack of research funds and seen as a heretic by some of the medical establishment for his unorthodox approach to hemangioma, Dr. Tan came out victorious despite the odds against him. He founded the Gillies McIndoe Research Institute which was officially opened by the Prime Minster of New Zealand in 2013. He now heads this institute in its pursuit to research into vascular anomalies, cancer, fibrotic conditions and regenerative medicine, based on the role of stem cells in disease and health, underpinned by his radical concepts.

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The CRM Bulletin is published four times a year with a print run of 3000 copies per issue. These are delivered free-of-charge 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 relevant to all stakeholders.

If you are seeking a means to reach out to the clinical research "ecosystem" in Malaysia, then talk to us about advertising your message in the CRM Bulletin.

Other publications by CRM

NCCR bulletin

Guide for Industry

Patient Brochure

MEDICAL RESEARCH ETHICS COMMITTEE 2015 UPDATES

The Medical Research Ethics Committee (MREC) which handles ethics approval for clinical research to be conducted in Ministry of Health Malaysia hospitals and institutions, is responsible for safeguarding the rights, safety and well-being of trial subjects. The committee seeks to ensure that the principles of confidentiality, informed consent, benefit and minimal risk are adhered to in research. In 2014, a total of 125 industry-sponsored research (ISR) was approved by the MREC, an increase of 23.8% from 2013. Of the total studies approved last year, 88% were full-board reviews, 7% were expedited and 5% exempt.

A full-board review (i.e. review conducted by a convened MREC committee) is required for studies that involve more than minimal risk (e.g. sensitive topics, unusual interventions), or involves vulnerable subjects who require special protection by the ethics committee (e.g. children, institutionalized people, pregnant women, cognitively impaired individuals, etc.). Studies can be approved as 'expedited' if the type of study involves no more than minimal risk to the subjects. Examples of expedited studies include research involving blood samples, focus group, program evaluation and collection of data through non-invasive procedures. The Ethics Committee conducts an exempt review if it is determined that the study places subjects at less than minimal risk. Examples of exempt studies include research involving surveys, interviews, existing data, public benefit of service program, etc. without links to subject identifiers.

MREC is administered by the National Institutes of Health

In early 2015, MREC made several changes to some relevant procedures in the NMRR system with the aim of improving the efficiency for the conduct of Industry Sponsored Research (ISR) in Malaysia. Salient points with regards to the changes made are as below:

MREC Notification and Acknowledgment of Receipt (AOR)

- Effective 9th January 2015, all documents for the purpose of MREC Notification and AOR are to be uploaded in the NMRR system. MREC would no longer be acknowledging documents received via e-mail, fax or courier/mail.
- Up to 32 different documents can be uploaded at a single submission and multiple submissions can be made to MREC at any given time. The document submission guideline (for the purpose of MREC notification) can be downloaded at https://www.nmrr.gov.my/doc/DOCUMENT%20SUBMISSION%20GUIDELINE.pdf
- Once submission via NMRR is completed, an immediate acknowledgement e-mail by nmrr@nmrr.gov.my will be sent to the Corresponding Person (CP). This is not to be confused with submission of amendment(s) which is sent separately and usually involves a decision letter.

Protocol Deviation Reporting

Effective 9th January 2015, all protocol deviations should be reported using the MREC Protocol Deviation or Violation Report form which is available in the NMRR webpage under User Manual/Documents.

SAEs/SUSARs Reporting Requirements

- Effective immediately, all local SAEs/SUSARs (involving all Malaysian sites) need to be reported to MREC. The timelines for reporting are as below:
  - SUSAR that is fatal/life threatening: Initial report must be made as soon as possible but not later than 7 calendar days from awareness of event by the investigator, followed by a complete report within 8 additional calendar days.
  - All other SUSARs/all local SAEs: Not later than 15 calendar days from awareness of event by the investigator.

In February 2015, the NMRR upgraded its MREC module on its system to include a separate submission for amendment, annual renewal and study closure to enable users to proactively monitor and update studies which have been closed or terminated. Users are required to key-in/upload amendments into separate tabs. Additionally, with this system upgrade, users would be able to track their study status via NMRR as each step of the review process will be updated. This would hopefully reduce the number of enquiries coming in on the status of the studies submitted.

CRM would like to highlight that communication with MREC is not solely limited to e-mails, as was reported otherwise in our previous issue (4th Issue). MREC still accepts phone communication especially if there are urgent issues to be attended to. However, please take note that e-mail communication is encouraged in order to ensure that queries and responses have been addressed correctly and to have a audit trail.

Clinical Research Malaysia Answers Your Questions

FAQ: Trial Budget Management

How can CRM assist Principal Investigators with their clinical trial budgets?

CRM, on behalf of the Principal Investigator (PI), can assist in negotiating a trial budget (as part of the clinical trial agreement) with a sponsor or CRO. CRM ensures that the fees paid are according to the current industry standards and are of fair market value, and will advise PIs if any fee needs to be revised. During the review of a trial budget, CRM ensures that all core components of a trial budget are addressed.

What is CRM's role in managing a clinical trial budget?

CRM acts as a trustee in managing a clinical trial budget by receiving and executing disbursement of the trial budget. Upon receiving a Payment Instruction Form from a PI, CRM releases payment to the relevant recipients (for purposes of patient reimbursement, lab tests/procedures, outsourcing services to vendors, investigators' fees, etc). Effective March 2015, CRM will pay the PIs directly instead of re-routing through the CRC Trust Account in HKL. This has shortened the payment timeline to less than 2 weeks, but if the relevant documents are in order and the cheque signatories are available, it is likely that for most cases the timeline will only take about a week. Apart from that, CRM ensures that a monthly Statement of Accounts is issued to the relevant Principal Investigators.

Why is it important for CRM to manage the trial budget?

CRM is authorized by the Malaysian Government to handle clinical trial budgets that are conducted in Malaysia. It is the role of CRM to ensure that payments are made to the relevant parties involved in the conduct of clinical trials and that it is made in a fair and transparent manner. According to the General Orders, Chapter D (Article 5), an Investigator, being a government officer, shall not receive money paid directly to him/her derived from his/her clinical trial activities. In light of this, CRM legitimizes the transfer of trial funds by managing the trial budget and channeling the investigators' fees to the relevant PIs.

Does CRM charge any fees for reviewing/managing a trial budget or CTA?

As a corporate entity providing services to investigators, sites and the clinical research industry, CRM has to generate income to sustain its operational costs. To do so, CRM charges the sponsor or CRO RM4000 per review of a CTA and a management fee of 15% of the value of the total trial budget to manage the trial budget.

Disclaimer: The information provided is correct at the time of publishing, but is subject to amendments or change depending on future circumstances.

CRM *in photos*

CRM Good Clinical Practice (GCP)
Workshop Selangor, 8th October 2014

CME: Nephrology Department,
Hospital Kuala Lumpur, 16th October 2014

Negeri Sembilan Research Day 2014
30th October 2014

Selangor Research Day 2014
10th November 2014

Prime Sites Meeting – JESC
14th November 2014

Karnival Kesihatan 2014 Hospital Taiping
12th November 2014

Dental Research Workshop
27th November 2014

Getting Started on Clinical Trials: Hospital Sg Buloh
27th November 2014

Melaka Research Day 2014
1st December 2014


CSR: CRM Flood Relief Support
2nd January 2015


CRM Dialogue with PIs
23rd January 2015

NCSM World Cancer Day Conference & Expo 2015
8th February 2015

8th Asia Regulatory Conference 2015
4th February 2015


NCCR Meeting Bengkel Semakkan Semula
Garispanduan Tisu Biologi Manusia Bagi
Tujuan Penyelidikan (sesi II), 3rd March 2015

Perak Annual Medical Research
Conference 2015, 6th March 2015

Pink Ribbon Life Beyond Breast Cancer
Teaching Symposium, 19th March 2015


1st Forum for Ethics Review Committee
in Malaysia, 30th March 2015

INDUSTRY News

Novartis' heart failure medicine LCZ696 granted FDA priority review

EAST HANOVER, N.J., Feb. 13, 2015 Novartis announced today that the US Food and Drug Administration (FDA) has granted priority review for LCZ696, an investigational medicine for the treatment of heart failure with reduced ejection fraction (HFrEF). The designation is intended to accelerate the review of therapies that offer a significant improvement in the safety or effectiveness of the treatment, prevention or diagnosis of a serious condition. For LCZ696, this reduces the total review time from 12 to 8 months, meaning the target FDA action date is in August 2015.

Source: www.drugs.com

GSK and Theravance Announce Start of Phase III Lung Function Study with 'Closed' Triple Combination Treatment FF/UMEC/VI for COPD

London UK and South San Francisco, CA - 09 February 2015 -- GlaxoSmithKline plc (LSE/NYSE: GSK) and Theravance, Inc. (NASDAQ: THRX) today announced the start of a second global phase III study to evaluate the effects of the investigational once-daily closed triple combination of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in patients with chronic obstructive pulmonary disease (COPD).

Source: www.drugs.com

Takeda Announces That the First Interim Analysis of the Phase 3 Study of Oral Ixazomib in Patients with Multiple Myeloma Met Primary Endpoint

Cambridge, Mass. and Osaka, Japan, February 10, 2015 – Takeda Pharmaceutical Company Limited (TSE:4502) today announced that the randomized, double-blind, placebo-controlled TOURMALINE-MM1 pivotal Phase 3 trial evaluating the safety and efficacy of ixazomib, the first oral proteasome inhibitor, conducted in patients with relapsed or refractory multiple myeloma (MM) achieved its primary endpoint of improving progression-free survival at the first pre-specified interim analysis. In the trial, patients treated with investigational ixazomib plus lenalidomide and dexamethasone lived without their disease worsening for a significantly longer time compared to patients who received placebo plus lenalidomide/dexamethasone.

Source: www.drugs.com

Pfizer Inc plans to acquire Hospira Inc for US$17 billion

Pfizer Inc. and Hospira, Inc. today announced that they have entered into a definitive merger agreement under which Pfizer will acquire Hospira, the world's leading provider of injectable drugs and infusion technologies and a global leader in biosimilars, for $90 a share in cash for a total enterprise value of approximately $17 billion. The Boards of Directors of both companies have unanimously approved the merger, which is expected to be immediately accretive upon closing, accretive by $0.10 - $0.12 per share for the first full year following the close of the transaction with additional accretion anticipated thereafter.

Source: www.pfizer.com

Malaysia is the second highest recruiter for the REDUCE study

Zwolle, The Netherlands – 2 February 2015 – Malaysia is once again the second highest recruiter after the Netherlands in the REDUCE study, a randomized controlled trial comparing dual antiplatelets therapy (DAPT) in acute coronary syndrome (ACS) patients at 3 months and 12 months after implantation of a new generation of coronary stent called COMBO. This study is currently being carried out in 6 different countries across Europe and Asia, with Malaysia being the highest recruiter in Asia.

Of the 203 patients recruited in Europe and Asia, Malaysia managed to successfully enroll 63 patients at four different sites. For two months consecutively, Dr. Liew Houng Bang and his study team from Queen Elizabeth II Hospital (Sabah) were the highest recruiter among these sites, with 29 enrolments. *Source: REDUCE Study Newsletter*

New drug for Alzheimer's Disease under trial

T-817MA is a new drug developed for treating Alzheimer's disease by scientists at Boston University Alzheimer's Disease Center and Boston Medical Center. The drug is reported to alter the course of the disease in patients already suffering from Alzheimer's dementia. If T-817MA works well in the trials, it would be the first drug approved for Alzheimer's disease after 2003 by the U.S. Food and Drug Administration (FDA). Dr. Robert Stern of the Alzheimer's Disease Center mentioned that he believes in T-817MA, among other drugs, even though slowing down the disease in someone who is already suffering from moderate stages of dementia is not that promising. The most-awaited drug, expected to help tens of thousands of people, is currently in the phase II of clinical trials.

Source: International Business Times (15 February 2015)

Dehydration linked to worsening stroke conditions

Patients who are dehydrated and suffer a stroke have worse short-term outcomes than those patients who are well-hydrated at the time of their stroke. Dehydrated patients had nearly a four times higher risk of worsening compared to patients who were adequately hydrated at the time of their stroke. Being well hydrated at the time of a stroke is associated with better outcomes.

Source: American Heart Association (12 February 2015)

Possible mechanism underpinning Alzheimer's and Parkinson's diseases

Scientists have for the first time discovered a killing mechanism that could underpin a range of the most intractable neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS. The new study revealed the mechanism of toxicity of a misfolded form of the protein that underlies prion diseases, such as bovine spongiform encephalopathy ('mad cow disease') and its human equivalent, Creutzfeldt-Jakob disease.

Source: Scripps Research Institute (12 February 2015)

Stem cell transplants may work better than existing drug for severe multiple sclerosis

Stem cell transplants may be more effective than the drug mitoxantrone for people with severe cases of multiple sclerosis (MS), according to a new study published in the February 11, 2015, online issue of Neurology®, the medical journal of the American Academy of Neurology.

Source: American Academy of Neurology (11 February 2015)

New therapeutic principle for Parkinsonian dyskinesia shows clinical effect

Involuntary dyskinetic movements induced by treatment with levodopa (L-dopa) are a common problem for people with Parkinson's disease. Now, however, researchers at Karolinska Institutet and Lund University in Sweden seem to be close to a novel therapy to this distressing side effect. A treatment study published in the scientific periodical Brain shows that a drug that stimulates certain serotonin receptors in the brain counteracts the dyskinesia causing effects of L-dopa. *Source: Karolinska Institutet (10 February 2015)*

About CLINICAL RESEARCH MALAYSIA

Clinical Research Malaysia (CRM) is a non-profit organization wholly owned by the Government of Malaysia. CRM was established in June 2012 to position Malaysia as a preferred global destination for industry-sponsored research (ISR), and to function as an enabler and facilitator to the industry and medical fraternity.

By working with other stakeholders, CRM strives to improve the local ecosystem to support growth in ISR, facilitate the needs and requirements of industry players, grow the pool of capable investigators, support staff and trial sites, and improve their capabilities and capacities to conduct ISR.

With the Ministry of Health's backing and clear knowledge of the local research environment, CRM is able to provide sponsors (primarily from the pharmaceutical, biotech and medical device industries) and contract research organizations (CRO) with an extensive range of services that includes feasibility studies, investigator selection, site research associates, management of trial budget, review of clinical trial agreements and updates on local laws, guidelines and regulations. CRM also undertakes marketing and promotional activities to build industry awareness about the opportunities for ISR in Malaysia, and create public and patient awareness of clinical trials.

Publish in the CRM bulletin

We welcome submissions of feature articles, write-ups and events related to industry sponsored clinical research for publishing in the CRM bulletin, which is issued quarterly. You can send your submission to contact@clinicalresearch.my or contact us at +60 3 7960 5153 should you have any queries. CRM has the right to edit any submission to suit the needs of the bulletin.

2015 UPCOMING NATIONAL & INTERNATIONAL EVENTS

Disclaimer: This list does not include all events that will be held in Malaysia or international.

National
International

MARCH

- 9th International Academic Conference in Otology, Rhinology & Laryngology (5th – 7th March, Kuala Lumpur)
- Coloproctology 2015 (12th – 15th March, Melaka)
- Preparatory Course for Clinical Examination Master of Paediatrics and 7th National Paediatric Research Conference (12th – 14th March, Kuala Lumpur)

APRIL

- Endoscopy 2015 (18th – 19th April, Selangor)
- 8th Asia Pacific Cleft Lip/Palate/Craniofacial Congress 2015 & 19th MAPACS ASM (23rd – 25th April, Penang)

MAY

- NCCR 9th National Conference for Clinical Research 2015 (27th – 29th May, Penang)
- College of Surgeon/AMM ASC 2015 (29th – 31st May, Penang)

JUNE

- Malaysian Society of Otorhinolaryngologists Head & Neck Surgeons Annual Scientific Meeting 2015 (4th – 6th June, Johor)
- 18th Annual Scientific Meeting of the Malaysian Society of Transplantation (4th – 6th June, Kuala Lumpur)
- International Digestive Disease Forum (6th – 7th June, Hong Kong)
- MSA & College of Anaesthesiologists Annual Scientific Congress 2015 & 13th Asian Society of Paediatric Anaesthesiologists Congress (11th – 14th June, Penang)
- Association of Private Hospitals of Malaysia (APHM) International Healthcare Conference and Exhibition 2015 (15th – 17th June, Kuala Lumpur)

JULY

- 11th Liver Update 2015 (30th Jul – 2nd Aug, Selangor)

AUGUST

- Annual Scientific Meeting of Intensive Care (14th – 16th Aug, Kuala Lumpur)
- 14th International Association of Endocrine Surgeons Course (19th – 21st Aug, Putrajaya)
- Singapore International Congress of O&G (20th – 22nd August, Singapore)
- GUT 2015 (21st – 23rd Aug, Johor)

SEPTEMBER

- 1st Asean Upper Gastrointestinal Surgical Conference & 4th Malaysian Upper Gastrointestinal Surgical Society Conference (11th – 13th Sept, Kuala Lumpur)

OCTOBER

- 2nd ISMINS Educational Meeting and 15th Neurosurgical Association of Malaysia Annual Scientific Meeting & Annual General Meeting (1st – 5th Oct, Kuala Lumpur)
- Asia Pacific NeuroEndocrine Tumour Society (APNETS) 2015 (30th – 31st Oct, Penang)

NOVEMBER

- Taiwan: Asian Conference for Emergency Medicine 2015 (7th – 10th Nov, Taipei)

DECEMBER

- 20th Congress of the Asian Pacific Society of Respirology 2015 (3rd – 6th Dec, Kuala Lumpur)
- European Society for Medical Oncology (ESMO) Asia Congress (18th – 21st Dec, Singapore)

1st Announcement

NCCR 2015

9th National Conference for Clinical Research 2015

27 – 29 MAY 2015 | BAYVIEW BEACH RESORT, PENANG, MALAYSIA

RESEARCH MATTERS TO SOCIETY

Block your dates! JOIN US!

MAIN CONFERENCE: 27 - 29 MAY 2015
PRE-CONFERENCE WORKSHOPS: 25 - 26 MAY 2015

Each year the conference brings to you renowned researchers and experts locally and internationally. Take full advantage to network. Explore new possibilities. Overcome boundaries. Think innovation. A little goes a long way as 'Research Matters to Society'.

FOCUS :

- Industry Sponsored research updates
- Geriatrics and gerontology - better living tomorrow
- Research that matters to public health via surveillance data and registry data

OBJECTIVES :

- To illustrate the vast research opportunity in the field of geriatric medicine and gerontology, from cellular to community
- To discuss and explore the need for the aging community, to generate knowledge for future research direction
- To emphasise the industrial role to focus on healthy aging and future neurocognitive research in the region of Asia
- To translate information from registry and surveillance data into actions with impact
- To generate the research passion in the young from the experience sharing from local and international research heroes
- To plan for a better living tomorrow through research

Look out for the tentative

PRE-CONFERENCE WORKSHOPS

25 – 26 MAY

- Healthcare Performance Workshop
- Evidence Based Medicine (EBM) Workshop
- Surgical/Medical Case Reports Writing Workshop

RESEARCH POSTER COMPETITION

Dr Wu Lien-Teh Research Awards

Submit by 3 April 2015

An opportunity to display your research, present research findings and obtain recognition for your work. Cash and medals await the winners:

Young Investigator Awards
(Oral Presentation)

- *First prize: RM 1000 + medal*
- *Second prize: RM 500*
- *Third prize: RM 250*

Best Poster Awards

- *First prize: RM 250 + medal*
- *Second prize: RM 200*
- *Third prize: RM 150*

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