CRM bulletin
A quarterly by Clinical Research Malaysia
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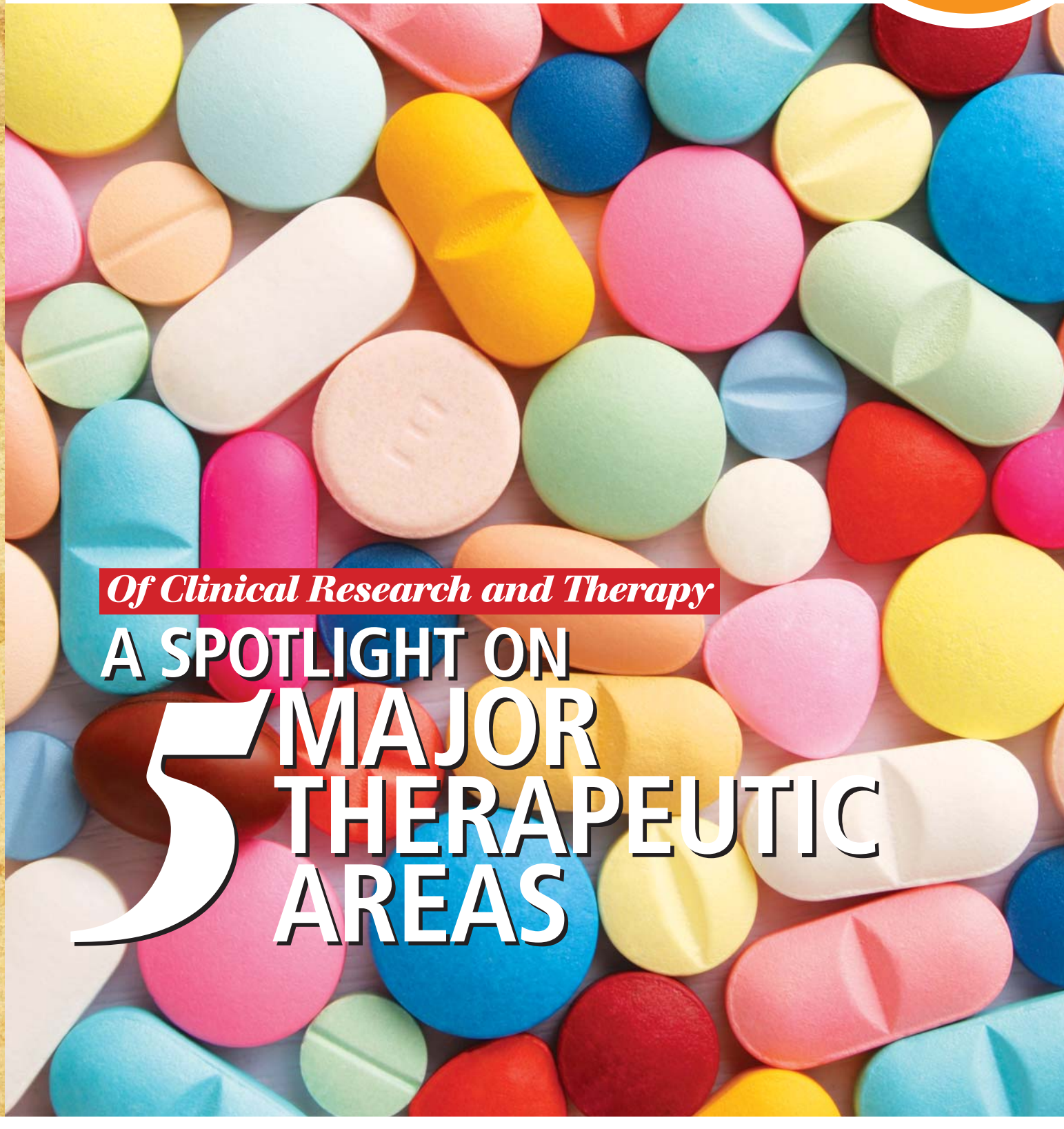
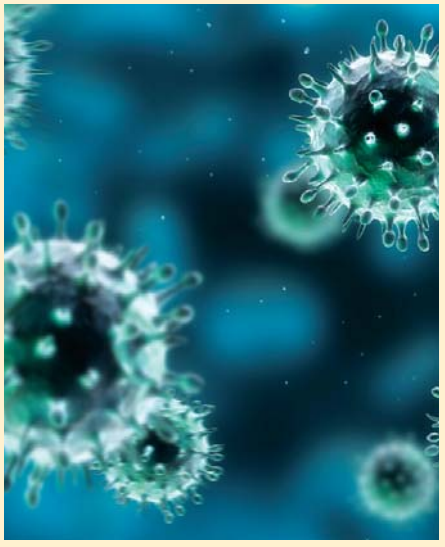
MAY 2013



Of Clinical Research and Therapy

A SPOTLIGHT ON 5 MAJOR THERAPEUTIC AREAS

CONTENTS



CONTRIBUTORS

We welcome healthcare professionals and postgraduate students with a keen interest in clinical research to share with us their ideas, views and articles in this field. Please email to contact@clinicalresearch.my

ABOUT US

Clinical Research Malaysia (CRM) is a company fully owned by the Government of Malaysia set up less than 10 months ago and it runs as a not for profit entity. The focus of the company is contract clinical research, with the vision to make Malaysia the preferred destination for the industry.

CRM'S FOCUS

- Improving sites by addressing their needs and allocating highly trained study coordinators. CRM will be actively managing six sites in 2013 while providing support for numerous others.
- Increasing investigators through mentoring programmes, training and awareness campaigns.
- Implementing strategies and procedures for feasibility assessments and investigator selections.
- Providing transparent and efficient trial budget management.
- Initiating collaborations with local, regional and global stakeholders.
- Impacting global pharmaceutical companies and clinical research organisations to invest in Malaysia.
- Inspiring private hospitals and universities to be part of this national agenda.
- Investigating and addressing the perception and awareness of clinical trials among healthcare professionals, administrators, patients and the public.

Read the CR evolution article on page 12 for CRM's history.

Clinical Research Malaysia (CRM)

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CRM
CLINICAL RESEARCH MALAYSIA
Your Global Solutions in One Nation

MINISTER OF HEALTH MALAYSIA

FOREWORD

As Medicine evolves, so should our knowledge and practices. Trust must be earned and if we want our people to believe in our care, trust in our ability and depend on our choices, our care must be evidence-based. Thus, I can assure you that the Malaysian Government's commitment will be consistent - we want clinical research to be nurtured as a culture amongst our doctors, dentists, nurses, pharmacists and other healthcare professionals.

I am pleased that, through the untiring efforts of our healthcare professionals, our country has a strong presence in clinical research within the region. We already have the right ingredients to be at the top of the ladder. Clinical Research Malaysia is here not because we were doing poorly; instead it was established because we can do better; together, we can develop what we have and acquire what we lack. We hope that you will be part of the programs that we are initiating. Making Malaysia the destination for clinical research is not a one-institution-show; it is a concerted team effort involving the public, private, and academia.

If you consider clinical research your calling, there is no time like the present to cultivate it.

> ***"We want clinical research to be nurtured as a culture amongst our doctors, dentists, nurses, pharmacists and other healthcare professionals."***

Dato' Sri Liow Tiong Lai
Minister of Health, Malaysia

20 March 2013

WELCOME...

This is the first edition of the CRM bulletin; it took almost 6 months to come to fruition but it is finally here. We hope all of you will find it useful, informative and perhaps in some ways, the bulletin will help to propagate clinical research in Malaysia.

The idea of the bulletin was conceived when the team in CRM was deliberating on its business plan. It was an exciting period; here we have a company set up primarily to make Malaysia the preferred destination to conduct contract research. The contract clinical research industry became a focus in Malaysia in the early 90s, striding along the years bringing about significant changes in the area that matters most, which is patient care, and causing changes in the regulatory and governing framework. CRM was to consolidate all these efforts, further strengthen the overall structure and systems and focus on bringing more contract research to Malaysia. The multiplier effect, which means both the direct and indirect effects of all these efforts, is to make research a culture among clinicians and all healthcare workers, and spearhead the development of all relevant industries of clinical research.

It is a tall order.

How then can the team in CRM communicate to all stakeholders of clinical research? The idea of a bulletin was coined, and now, by God's grace, the inaugural edition is out.

We are very enthusiastic about this bulletin. We feel it should strive to provide a concise update on the ins and outs of Clinical Research, be a source of information to gain valuable knowledge; we hope to do this by developing each issue with a specific theme. For the first issue, we provided an outlook of five top therapies for clinical research globally. In subsequent issues, we hope to share stories of local research personnel and highlight the key ingredients of their successes. At times, the overall scheme of everything seems very complicated, but we at CRM have learned that beneath all these complexities lie fundamental basic simple processes, values and tools that in consistent usage result in spectacular outcomes. We are still learning and are humbled by the dedication and commitment of the individuals and teams of this research fraternity. We are hoping too, that in a small way, this bulletin would bring about a change for better inculcation of clinical research and assist you in making informed decisions in the area of clinical research.

We would like share some ideas propagated by Thomas Kuhn in his 1962 essay, 'The Structure of Scientific Revolutions'. He states that shared beliefs are required by the scientific community to practice its trade. Kuhn argues that research is 'a strenuous and devoted attempt to force nature into the conceptual boxes supplied by professional education'.

> ***"This bulletin would bring about a change for better inculcation of clinical research and assist you in making informed decisions in the area of clinical research..."***

We have learned from the examples around us over the last decade of failed corporations, financial disasters, man-made catastrophes and evolving challenges in the development of new therapies and increasing demand on the healthcare systems. It is time to let go of our out-moded thinking and give up inaccurate conceptual models. It is time to build realistic assumptions and reevaluate prior facts. On a less serious note, be wary of management catch phrases, such as 'think outside the box' and 'blue ocean', as these may provide a false impression of being smart and savvy, but in reality, nothing is changed.

We will work with all of our stakeholders, move beyond the existing nuances, and realise the aspirations of the nation.

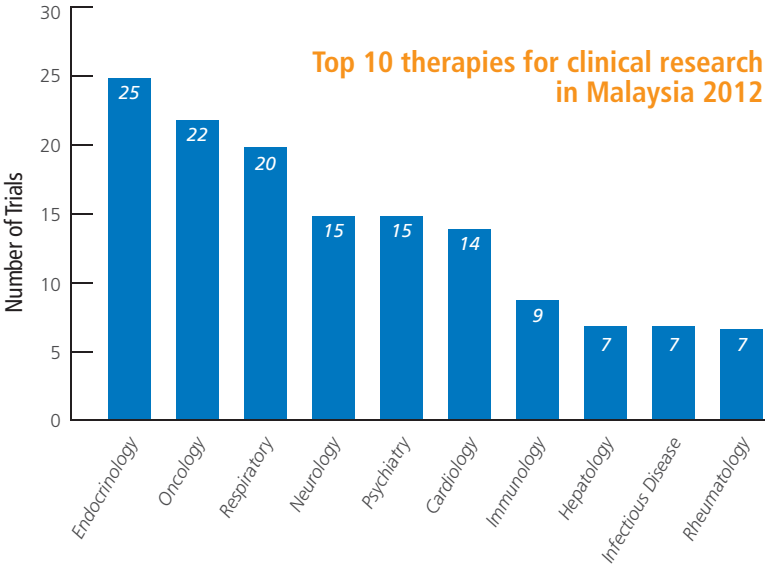
Insya Allah.

Dr Mohamed Ali Abu Bakar
CEO, Clinical Research Malaysia

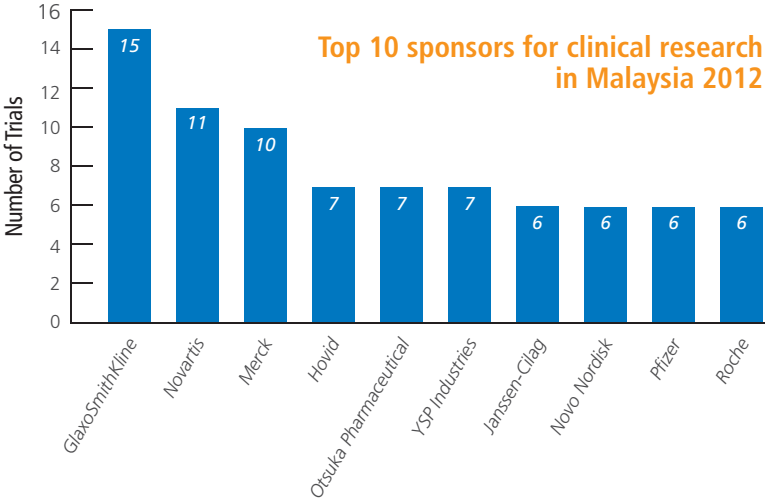
CRstats@my

179 contract clinical research were approved by the various ethics committees in Malaysia in 2012. These trials were conducted in public hospitals, universities and private hospitals.

Top 10 therapies for clinical research in Malaysia 2012



Top 10 sponsors for clinical research in Malaysia 2012



CRM thanks the following for contributing their data

1. National Medical Research Register
2. Hospital Universiti Kebangsaan Malaysia
3. Hospital Universiti Sains Malaysia
4. Institute Jantung Negara
5. International Medical University
6. Joint Penang Independent Ethics Committee
7. Ministry of Health Medical Research and Ethics Committee
8. Sime Darby Medical Centre
9. Sunway Medical Centre
10. Universiti Islam Antarabangsa
11. Universiti Teknologi MARA
12. University Malaya Medical Centre
13. Universiti Putra Malaysia
14. University Sains Malaysia – Lam Wah Ee

Of Clinical Research and Therapy

A SPOTLIGHT ON 5 MAJOR THERAPEUTIC AREAS

Trials in Malaysia

Twenty-two contract research were approved in 2012. These include clinical trials on prostate cancer, breast cancer, colon cancer, colorectal cancer and multiple myeloma.

➤ *www.nmrr.gov.my and the various ethics committees in Malaysia*

No. of Global Clinical Trials in Specific Conditions in 2013

• Neoplasms	(n=15848)
• Leukemia	(n=13221)
• Lymphoma	(n=11361)
• Multiple Myeloma	(n=8300)
• Breast Cancer	(n=6277)
• Melanoma	(n=4965)
• Lymphoma, B-Cell	(n=4950)
• Neoplasm Metastasis	(n=4673)
• Non-Small Cell Lung Cancer	(n=2716)
• Prostate Cancer	(n=2594)
• Adenocarcinoma	(n=1835)
• Colorectal Cancer	(n=1661)
• Hematologic Neoplasms	(n=1623)
• Lung Cancer	(n=1243)
• Sarcoma	(n=1166)
• Ovarian Cancer	(n=1151)

➤ *www.centerwatch.com*

ONCOLOGY
***95,000** trials*

NEUROLOGY
***36,000** trials*

INFECTIOUS DISEASE
***20,000** trials*

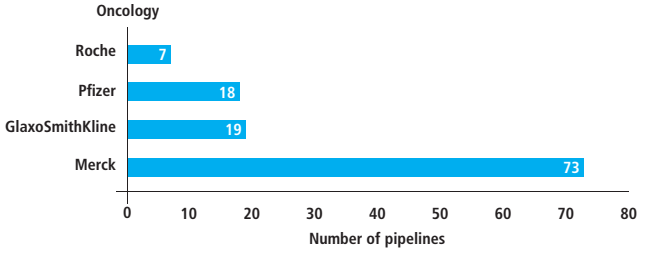
CARDIOLOGY
***47,000** trials*

ENDOCRINOLOGY
***30,000** trials*

➤ *www.centerwatch.com*

May 20th is International Clinical Trials Day. Researchers commemorate it as the day James Lind began his famous skurvy trial in 1747. And we will commemorate it in this pioneering issue by featuring five major therapies for clinical trials; examining their studies, stats, news and facts.

1. ONCOLOGY



➤ *Source: Each companies' websites (March 2013)*

Significant Oncology

Achievements in the field of oncology clinical research from year 2000.

2001
- Gleevec, a drug that can inhibit the actions of a gene, is approved by FDA for treatment of chronic myelogenous leukemia.

2002
- Femara, a hormone therapy drug, was approved by FDA for treatment of advanced breast cancer.
- New screening test for colon cancer that detects specific genetic abnormalities in stool samples of up to 70% of patients with colon cancer.

2004
- Erbitux, a monoclonal antibody, was approved by FDA for treatment of colon cancer
- Avastin, an anti-angiogenesis drug, was approved by FDA for treatment of colocteral cancer.

2006
- Gardasil was approved by FDA as a vaccine against the virus that causes cervical cancers.

➤ *www.webmd.com*

FDA Approved Drugs in 2013

Kadcyla (ado-trastuzumab emtansine)	For HER2-positive metastatic breast cancer
Pomalyst (pomalidomide)	For relapsed and refractory multiple myeloma
Stivarga (regorafenib)	For gastrointestinal stromal tumor

www.centerwatch.com

WHAT'S NEW

MALAYSIA

• Not Light Years Behind

Photodynamic therapy may be more beneficial as a cancer treatment than surgery, radiation and chemotherapy in terms of less body toxicity and resistance. This new method of treatment uses special drugs that are sensitive to light. According to Prof LY Chung from the University Malaya's (UM) Department of Pharmacy, the drug is given some time to be absorbed by cancer cells before light is shone to the areas that need to be treated. This causes the drug to react with oxygen and develop a chemical that destroys cancer cell.

Source: Chemical Society Review Journal 2013; 42:77-88

WORLD

• No Collaboration, No Progress

More than half of the 120 urothelial cancer trials registered on Clinicaltrials.gov involved three sites or fewer, according to Matthew D. Galsky, assistant Professor of Urology at Mount Sinai Hospital. He and his colleagues also found that of the 56 trials that completed enrolment, the median time to complete accrual was 50 months. These trials enrolled a median of 40 patients per trial. Dr Galsky identified the lack of communication and collaboration as barriers to the development of more effective therapies in urothelial cancer.

Source: HemOnc Today 2013 (http://www.hemonctoday.com/pdaArticle.aspx?rID=105134)

• Next-Generation Clinical Trials

"We don't need a magic bullet, we need a magic shotgun", says George Sledge, chief of the Oncology Division at Stanford University School of Medicine in California, when asked about developing new therapies. The "smart" cancers are those that show multiple mutational drivers with a large mutational load. Such cancers like lung cancer and melanoma need multitargeted therapy. Today's clinical trials system is not keeping with the progress in cancer genomics. Designs of trials should consider multitargeting, as we are now able to measure the emergence of compensatory mechanisms of resistance.

Source: OncLive 2013 (http://www.onclive.com/conference-coverage/mbcc-2013/Oncology-Enters-Era-of-Genomics-Sledge-Calls-for-Overhaul-of-Clinical-Trials-System)

• Abiraterone Acetate Improves Overall Survival

A study on metastatic prostate cancer revealed that abiraterone improved radiographic progression-free survival. It showed a trend towards improved overall survival, and significantly delayed clinical decline and initiation of chemotherapy in patients with metastatic castration-resistant prostate cancer.

Source: New Eng of Med 2013;368:138-48

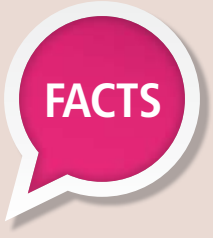
• Conventional or High-Dose Chemotherapy with Rituximab?

A research was done to investigate whether conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab improved survival outcome for young patients with high-risk aggressive B-cell lymphoma. R-MegaCHOEP was not superior to conventional R-CHOEP therapy and was associated with significantly more toxic effects. R-CHOEP-14 with or without radiotherapy remains a treatment option for these patients, with encouraging efficacy. *Source: Lancet Oncol. 2012;13:1250-9*

• EGFR Immunoliposomes Have Antitumour Effects

A phase 1 dose-escalation study showed that the EGFR immunoliposomes have substantial antitumour effects. Because anti-EGFR ILs-dox was well tolerated, further assessment of this nanoparticle at recommended dose in phase 2 trials have been warranted. *Source: Lancet Oncol. 2012;13:1225-33*

2. CARDIOLOGY



Trials in Malaysia

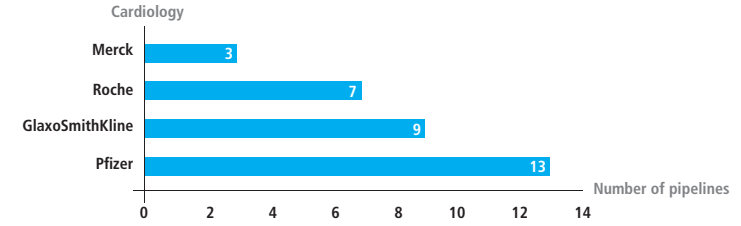
Fourteen contract research were approved in 2012. These include trials on familial hypercholesterolemia, pulmonary arterial hypertension, essential hypertension, and corronary artery disease.

➤ *www.nmrr.gov.my and the various ethics committees in Malaysia*

No. of Global Clinical Trials in Specific Conditions in 2013

- Atrial Fibrillation (n=12935)
- Heart Failure (n=8049)
- Stroke (n=6299)
- Atherosclerosis (n=5201)
- Coronary Artery Disease (n=4350)
- Cystic Fibrosis (n=1414)
- Vascular Diseases (n=1375)
- Venous Thrombosis (n=1282)
- Venous Thromboembolism (n=1185)
- Thromboembolism (n=1080)

➤ *www.centerwatch.com*



➤ *Source: Each companies' websites (March 2013)*

Significant Cardiology

Landmark trials in the field of cardiology in 2012.

- **ARISTOTLE:** Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation
- **C PORT E:** Atlantic Cardiovascular Patient Outcomes Research Team–E Trial
- **FAME 2:** Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2
- **FREEDOM:** Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease
- **JUPITER:** Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
- **MADIT-RIT:** Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate Therapy
- **PARTNER Cohort A:** Placement of Aortic Transcatheter Valves (Cohort A): TAVR vs. Surgical AVR
- **PHS II:** The Physicians' Health Study II
- **PRODIGY:** PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study
- **STAMPEDE:** Surgical Treatment and Medications Potentially Eradicate Diabetes Effectively
- **SORT OUT III:** Comparison of Zotarolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease
- **SPS3:** Secondary Prevention of Small Subcortical Strokes
- **Symplicity HTN-2:** Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension

➤ *www.cardiosource.org*

FDA Approved Drugs in 2013

Kynamro (mipomersen sodium)	For homozygous familial hypercholesterolemia

www.centerwatch.com

WHAT'S NEW

WORLD

• A Major Flaw?

Using niacin for heart disease is considered outdated by today's standard. A trial which involved 25,673 patients discloses unfavourable outcome as researches presented data which has proven that niacin is responsible for increasing diabetes complications, bleeding and infections in heart patients and did not prevent heart attacks and strokes.

Source: Medical News Today 2013 (http://www.medicalnewstoday.com/articles/257472.php)

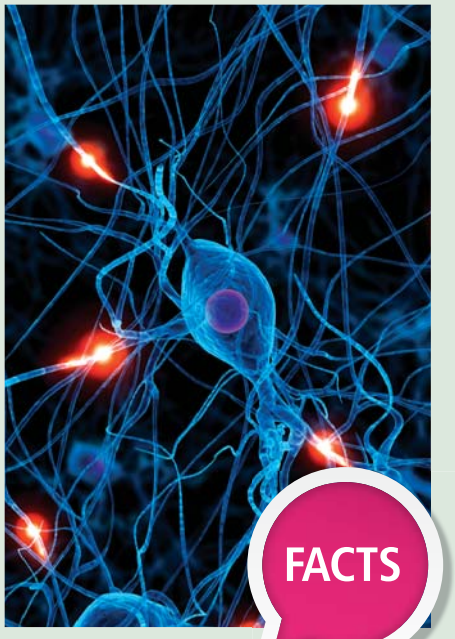
• Effective Strategies for the Prevention of Contrast-induced Nephropathy

A randomized clinical trial was conducted to discover the efficacy of oral hydration in the prevention of contrast-induced nephropathy in 120 patients undergoing elective coronary invention. The patients were randomly assigned to three groups. Group A was given intravenous hydration before and after coronary angiography or angioplasty. Group B was given oral tap water before and after the procedures, whereas group C was given only post procedural drinking water. The incidence of contrast-induced nephropathy in group A, B and C was 5.0%, 7.5% and 5.0% respectively. Renal function in the seven patients who experienced contrast-induced nephropathy recovered within a week following rehydration treatment. The comparison of oral and intravenous hydration strategies showed that both were effective in the prevention of contrast-induced nephropathy in patients undergoing coronary angiography or angioplasty. *Source: Acta Cardiol. 2012;67:565-9*

• Positive Key Health Outcomes for the Elderly Male

Testosterone supplementation during exercise rehabilitation is possible and can positively impact a range of key health outcomes in elderly male patients with chronic heart failure who have low testosterone status. Preliminary data were recorded for key health outcomes during a 12-week programme of exercise. It was observed in patients who completed the study that attrition was 30% with 100% compliance to exercise and injections. Similar improvements were also observed in shuttle walk test, body mass and hand grip strength. The testosterone group showed improvement in peak oxygen uptake, Beck Depression Inventory, leg strength, and several Medical Outcomes Study Short-Form quality of life domains, which were not observed in the placebo group. However, echocardiographic measures, N-terminal pro-brain natriuretic peptide, and inflammatory markers remain mostly unchanged. *Source: Am Heart J. 2012;164:893-901*

3. NEUROLOGY



FACTS

Trials in Malaysia

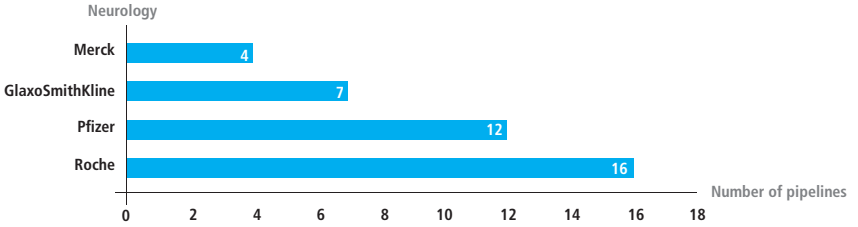
Fifteen contract research were approved in 2012. These include trials on multiple sclerosis, SLE, severe traumatic brain injury, Parkinson's disease and Alzheimer's disease.

➤ *www.nmrr.gov.my and the various ethics committees in Malaysia*

No. of Global Clinical Trials in Specific Conditions in 2013

- Multiple Sclerosis (n=7753)
- Stroke (n=6305)
- Depression (n=5962)
- Epilepsy (n=4892)
- Pain (n=1628)
- Bipolar Disorder (n=1495)
- Sleep Apnea Syndromes (n=1188)
- Meningitis (n=980)
- Alzheimer's Disease (n=886)
- Aneurysm (n=745)
- Fibromyalgia (n=561)
- Dementia (n=506)
- Dyskinesias (n=358)
- Anxiety Disorders (n=308)

➤ *www.centerwatch.com*



➤ *Source: Each companies' websites (March 2013)*

WHAT'S NEW

MALAYSIA

• Keeping Awake

University Malaya Specialist Centre signed a memorandum of understanding with PHILIPS Malaysia to set up a centre for sleep disorders in Malaysia. The ASEAN Sleep Research & Competence Centre (ASRCC) would be South East Asia's first and will be housed at the University Malaya Specialist Centre. The centre will involve a unit for clinical research, which will study sleep disorders among Asians. Although sleep disorders are under-diagnosed, they significantly impact a person's physical, mental and emotional well-being, and are especially linked to road accidents. Almost half of the bus drivers surveyed by the Malaysian Institute of Road Safety Research had sleep disorders. A common sleep disorder, Obstructive Sleep Apnoea (OSA), affects 4.1-7.5% of middle-aged men and 2.1-3.2% of middle-aged women. This condition is linked to obesity, hypertension and heart failure. The ASRCC is expected to open in July 2013.

Source: Medical Tribune 2013 (http://www.mims.com.my)

WORLD

• Stopping the Cause Instead of the Effect

A phase I trial on an investigational drug for inherited form of amyotrophic lateral sclerosis (ALS) has shown no serious side effects. The drug which is introduced into the central nervous system switches off the mutated gene, SOD1, which causes the disease. Ten percent of ALS are linked to inherited mutations; 2% of which are caused by mutations to the SOD1 gene. As over 100 mutations in the SOD1 gene can cause ALS, the focus of this study is to stop the production of the SOD1 protein instead of finding out how each of the mutations causes ALS. This approach can be useful for some forms of Alzheimer's disease, Parkinson's disease and Huntington's disease.

Source: Lancet Neurology 2013;12:435-42

• Tai Chi for Parkinson's Disease

One-hundred and eighty five patients with Parkinson's Disease were randomised to be trained in tai chi, resistance training and stretching twice a week for 6 months. Each session was for one hour. After 6 months, the patients who were doing tai chi had better postural stability than the other two groups. The tai chi group also had significantly fewer falls than the group that did stretching but not significantly fewer than the resistance group.

Source: New Eng J Med 2012; 366:511-9

• Recruitment Strategy

Retrospective analyses of six Alzheimer's Disease Cooperative Study (ADCS) randomised clinical trials found that there more were participants (67%) with spouses who enrolled than participants with adult children (26%) or other study partners (7%). Participants with spouse partners had a significantly lower dropout rate (25%) than participants with other study partners (34%), but not significantly lower than those with adult children (32%).

Source: Neurology 2013;80:282-8

4. ENDOCRINOLOGY

FACTS

Trials in Malaysia

Twenty-five contract research were approved in 2012. Most of the trials were on diabetes.

➤ *www.nmrr.gov.my and the various ethics committees in Malaysia*

No. of Global Clinical Trials in Specific Conditions in 2013

- Diabetes Mellitus, Type 2 (n=22037)
- Ovarian Cancer (n=1174)
- Diabetes Mellitus, Type 1 (n=746)
- Endometriosis (n=702)
- Pancreatic Cancer (n=461)
- Acromegaly (n=436)
- Obesity (n=360)
- Hyperparathyroidism (n=335)
- Infertility (n=248)
- Diabetic Retinopathy (n=240)
- Hypogonadism (n=226)

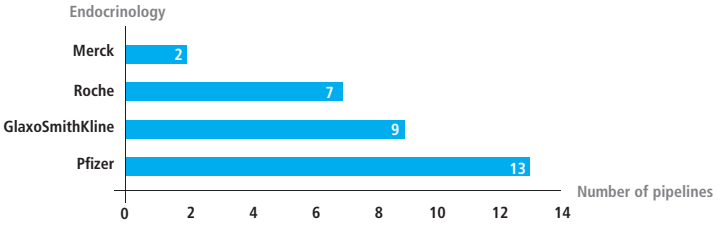
➤ *www.centerwatch.com*

Significant Diabetes

Several members of the American Diabetes Association and The Endocrine Society were chosen to review the recent evidence of the effect of hypoglycaemia on diabetes and provide guidance on how this should be included in clinical practice. The report was approved in November 2012 and is based on published data from latest clinical trials and other studies. It covers the following:

- Confirmed existing definitions of hypoglycaemia in diabetes
- Assessed the short-term and long-term effects of hypoglycaemia
- Reviewed the effects of hypoglycaemia on treatment outcomes
- Introduced approaches to prevent hypoglycaemia
- Identified knowledge gaps for future research
- Presented tools for patients to report hypoglycaemia at each visit and for clinicians to document counseling

Source: Journal of Clinical Endocrinology & Metabolism



➤ *Source: Each companies' websites (March 2013)*

WHAT'S NEW

WORLD

• Fructose vs Glucose

Increases in fructose consumption were linked to the increasing prevalence of obesity, and high-fructose diets are thought to promote weight gain and insulin resistance. Results revealed that consumption of fructose compared with glucose resulted in a distinct pattern of regional cerebral blood flow and a smaller increase in systemic glucose, insulin, and glucagon-like polypeptide 1 levels. *Source: JAMA 2013;309:63-70*

• Jianpi Huatan Fang to Treat Liver Disease

A study was done on the efficacy of the Chinese medicine Jianpi Huatan Fang in treating non-alcoholic fatty liver disease in children. Sixty children patients with non-alcoholic liver disease were randomly assigned to two groups of 30 patients, each being treated with Jianpi Huatan Fang and the Vitamin E Recipe within the span of 3 months, respectively. The Chinese medicine group saw a higher total effective rate of 83.3% compared to the Vitamin E group with only 46.7%. In addition, after the treatments, both groups saw significant decrease of the levels of serum lipid metabolic indexes and insulin resistance indexes. Both treatments could effectively enhance the function of the liver, but the Chinese medicine group showed better efficacy. The results of the study were positive, showing no observable toxic side effects.

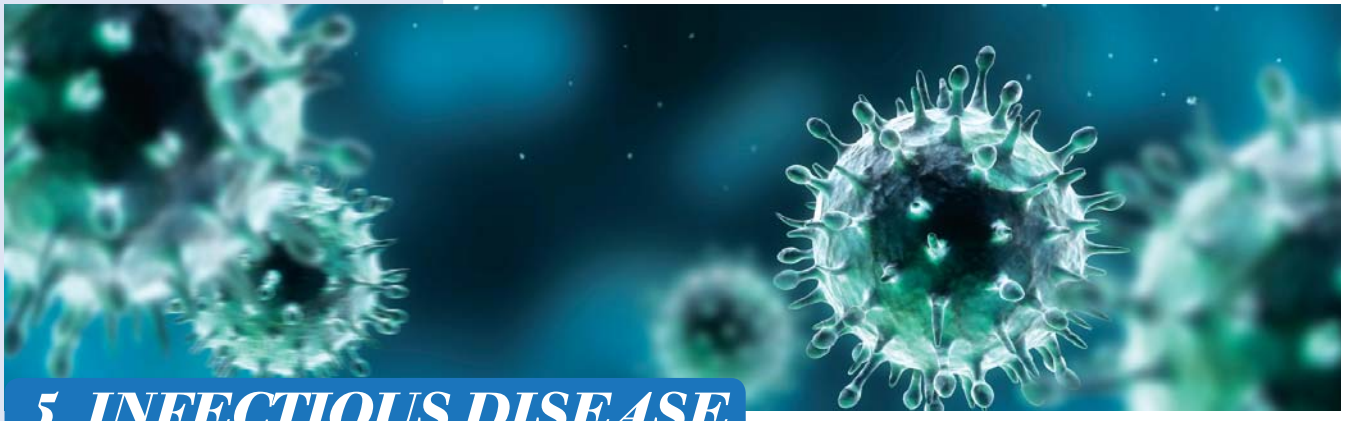
Source: Zongguo Zhong Yao Za Zhi 2012;37:2465-8

• Prevention Should Be Better than Cure

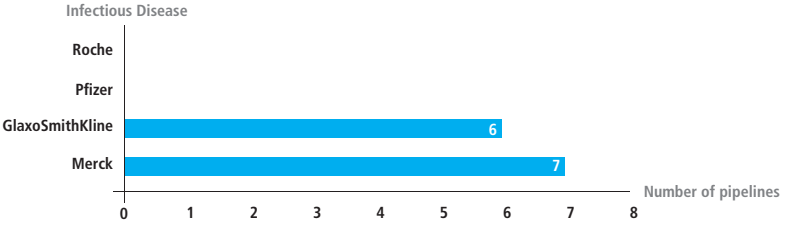
A study that analysed 2,500 diabetes-related trials found that there were far more research on drug therapies than preventive strategies. This study, which was the initiative of the U.S. Food and Drug Administration and Duke University, found that 63% of the research was on drug therapies, 12% on behavioural interventions and a mere 10% on preventive measures. In its aims to identify ways to improve clinical trials, the study indicated that most clinical trials had a small number of patients at a limited number of sites, were completed in less than two years, and were not geographically diverse. Only 1% of trials were primarily focused on older people and 4% were aimed at people aged 18 and younger. *Source: Diabetologia 2012 (DOI 10.1007/s00125-013-2890-4)*

• Look to the Liver for Hope

Animal studies have found that betatrophin, a liver hormone, has the potential to treat diabetes. Researchers conclude that monthly (or even yearly) betatrophin injections could stimulate the pancreatic cells to provide the same level of blood-sugar regulation for people with type 2 diabetes as daily insulin injections. They also suggested that the treatment to cause fewer complications. Currently, work is underway to discover the hormone's receptor and mechanism of action. The compound will be ready for clinical trials in two years. *Source: Nature 2013 (doi:10.1038/nature.2013.12878)*



5. INFECTIOUS DISEASE



➤ *Source: Each companies' websites (March 2013)*

FACTS

Trials in Malaysia

Seven contract research were approved in 2012. These include clinical trials on HIV, infections in the intensive care unit, and human papillomavirus.

➤ *www.nmrr.gov.my and the various ethics committees in Malaysia*

No. of Global Clinical Trials in Specific Conditions in 2013

- Hepatitis (n=7581)
- HIV Infections (n=4774)
- Hepatitis B (n=1148)
- Meningitis (n=980)
- Inflammation (n=774)
- Aspergillosis (n=557)
- Inflammatory Bowel Disease (n=495)
- Irritable Bowel Syndrome (IBS) (n=494)
- HIV (n=465)
- Influenza (n=313)

➤ *www.centerwatch.com*

FDA Approved Drugs in 2013

Flublok (seasonal influenza vaccine)	for the active immunisation against influenza virus subtypes A and type B
Sitavig (acyclovir) buccal tablets	for the treatment of recurrent herpes labialis in adults
VariZIG, Varicella Zoster Immune Globulin (Human)	for the post-exposure prophylaxis of varicella zoster (chickenpox)

Significant Malaria

In conjunction with World Malaria Day in April, the National Institutes of Health (NIH), US, reinstated its commitment in researching Malaria, a disease that kills about 660,000 people worldwide. The NIH research initiatives include:

- The identification of a new class of anti-malaria compounds that target multiple stages of the malaria parasite's lifecycle.
- Early stage testing for the anti-malaria drug DSM265 in 2013.
- A phase II clinical trial of the novel anti-malaria drug NITD609.
- Studies on understanding the immunology and disease progression of malaria in pregnant women and young children.
- Studies on the effect of malaria on HIV treatments in co-infected individuals.
- Tests on seven vaccine candidates. Results on one candidate vaccine that uses live, weakened malaria parasites delivered intravenously to prompt an immune response are expected in 2013.

Source: www.nih.gov

WHAT'S NEW

MALAYSIA

• Vaccine for Dengue Almost a Reality

Sanofi has completed a phase III trial on its tetravalent CYD dengue vaccine in Malaysia in January this year. Two-hundred and fifty healthy children between the ages of 2 and 11 were recruited from four sites (Ipoh, Kuala Lumpur, Sarawak and Negeri Sembilan). Informed signed consent was obtained from their parent or a legally acceptable representative. The participants were randomised with one group receiving three doses of the vaccine and the other group receiving three doses of saline. This 2-year study looked at the safety and immunogenicity of the vaccine. Results of this study will be available soon.

Source: Clinicaltrials.gov (http://www.clinicaltrials.gov./ct2/show/NCT01254422?term=sanofi+dengue+vaccine+healthy+children&rank=5)

• Malaysia, the First Asian Country to Host HIV Conference

Malaysia will be the venue for the 7th International AIDS Society (IAS) Conference on HIV. This biannual event will be organised by the International AIDS Society and University Malaya from June 30 to July 3 2013 in Kuala Lumpur Convention Centre. This is the first time the conference is being held in Asia. The 4-day event will discuss HIV-related research. Based on previous conferences, 5000 delegates from across the globe are expected. The conference will feature distinguished researchers, scientific leaders and clinical experts.

Source: http://www.ias2013.org/

WORLD

• Following Leprosy for Six Years

A 6 years follow-up study of the effectiveness of rifampicin chemoprophylaxis in a clinical trial cohort in Bangladesh indicated a 57% decline in leprosy incidence among contacts of newly diagnosed patients. The cohort consists of 1,037 patients and their 28,092 contacts participated in the randomised placebo controlled field trial. It was observed that the protective effect of chemoprophylaxis with single dose of rifampicin (SDR) emerged only in the first 2 years, with no additional effect after 4 and 6 years. However, the overall impact of the intervention was still statistically significant after 6 years and subsequently no excess cases were observed. Leprosy was restrained in contacts who received SDR.

Source: Lepr Rev. 2012;83:292-304

• Setback to the HIV Vaccine Pursuit

The HVTN 505 study was a trial on an investigational prime-boost vaccine regimen developed by the United States National Institute of Allergy and Infectious Disease. The 4-year study, which recruited over 2,000 volunteers from 19 US cities, was halted by an independent data and safety monitoring board recently as they found 41 cases of HIV infection in those that received the vaccine compared to 30 infection cases among those who received placebo. The vaccine also failed to reduce viral load among those who were HIV positive prior to entering the study.

Source: US National Institute of Allergy and Infectious Diseases (April 25 2013 Statement)

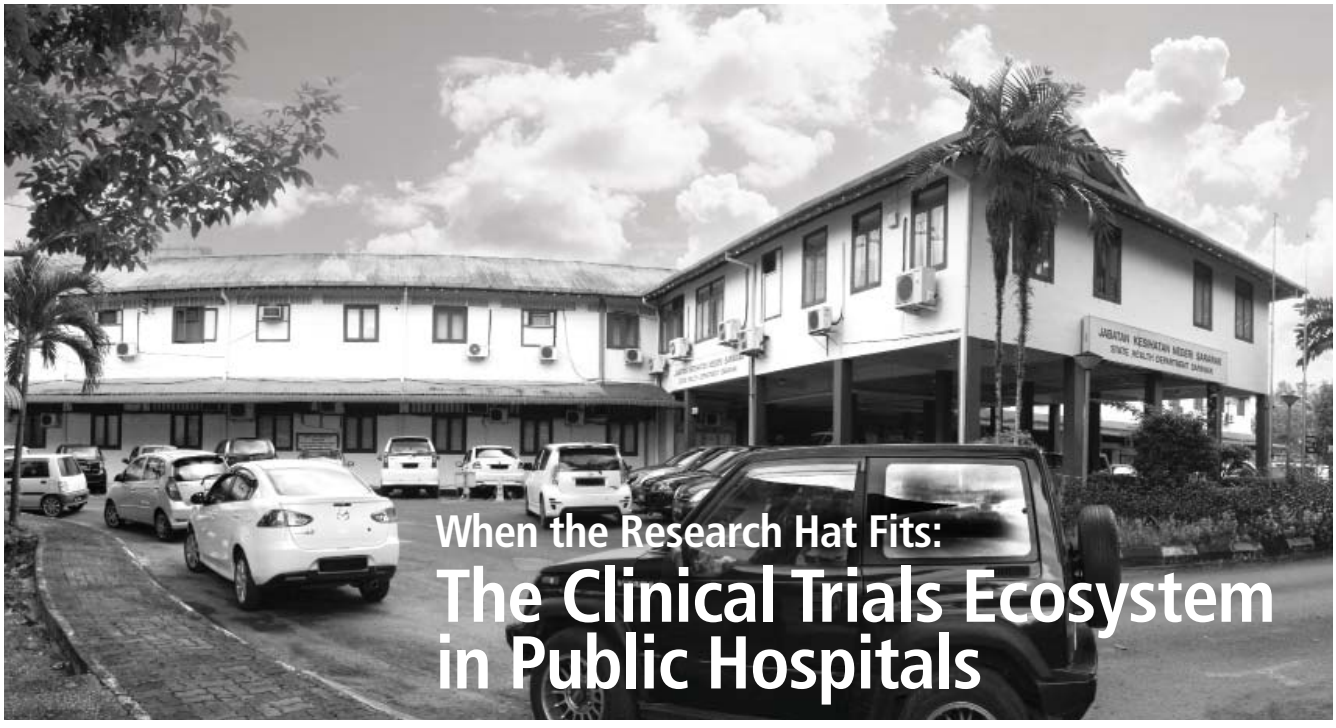
• Antibiotics Not Catching Up with Infections

The Infectious Diseases Society of America (IDSA) has approved only two new antibiotics since 2009 although infections caused by antibiotic-resistant bacteria are rapidly increasing and causing significant morbidity and mortality. They also identified seven drugs in clinical development for treatment of infections caused by resistant gram-negative bacilli (GNB) but none of these focus on the entire range of clinically relevant GNB resistance. The IDSA introduced its 10x'20 initiative to tackle the serious lack of progress in this area. Its aim is to form a global collaboration for antibacterial drug research and development with the capability to produce ten novel systemically administered antibiotics that are safe and efficacious by 2020. *Source: Clin Infect Dis. 2013 (10.1093/cid/cit152)*

• Merck Partners Bristol-Myers Squibb for Trial

Two of the major pharmaceutical companies, Merck and Bristol-Myers Squibb, will be collaborating on a chronic hepatitis C trial. The study will consist of a once-daily oral combination regimen of Bristol-Myers Squibb's experimental drug, daclatasvir and Merck's experimental therapy, MK-5172. Daclatasvir is a NS5A replication complex inhibitor while Merck's MK-5172 is an NS3/4A protease inhibitor. The agreement, which was to identify novel oral regimens early, stated that Merck will carry out the phase II trial at the completion of this phase I trial.

Source: FirstWord PHARMA 2013 (http://www.firstwordpharma.com/node/1075906)



When the Research Hat Fits:
The Clinical Trials Ecosystem in Public Hospitals

This is the first in the series of articles that will look into the development of Malaysia's Clinical Trials Ecosystem. In this issue, we examine how clinical research evolved in the Ministry of Health.

In the Beginning *(1980-1990)*

Committed clinicians but lack of trial knowledge, support, infrastructure and regulation.

Our story begins more than 30 years ago, in an institution over a century old. The Institute for Medical Research (IMR) established in the 1900s is Malaysia's pioneering research institute for medicine. It primarily does biomedical research, but IMR also set up a Clinical Research Centre in 1982 to research blood disorders, sexually transmitted diseases and myeomas on outpatients.[1] Although there were no dedicated centre for industry sponsored research, the U.S. Food and Drug Administration (FDA) reported that Malaysian clinicians have been doing clinical trials since the 80s.[2] Dr Ismail Merican, the Director-General of Health, in his speech during the 2007 National Conference for Clinical Research, described research during these early days as fragmented.[3] There was very little support and guidance and clinical research were small projects conducted by committed clinicians. The industry sponsored research that was conducted were primarily studies in phase IV.[2] These are mostly studies initiated by the local or regional marketing department of pharmaceutical companies. The drug or treatment is tested after it has been marketed to compile information on the drug's effect in various populations and any side effects associated with long-term use.[4] The US companies were reluctant to outsource phase II or early phase III trials to other countries as the FDA was wary of non-US data.[2] The companies were not prepared to put in resources overseas if the data from these countries are not allowed to be used for their new drug applications.

The Roaring 90s (1990-2000)

Global acceptance, improved local awareness and the start of better regulation. But lack of coordination and structure, and limited researchers.

Better acceptance of global clinical trial data began in 1996 with the International Conference on Harmonization (ICH) Good Clinical Practice.[5] The ICH GCP is a uniformed standard for the US, European Union and Japan. With the ICH, regulatory bodies started accepting clinical data from countries within these jurisdictions. Malaysian investigators also had more opportunities to conduct phase II and III trials. But Malaysia had yet to implement Good Clinical Practice and the approval processes for ethics and regulatory were unclear. Approval for ethics at that time could take as long as 9 months. Dr Amar Singh, well-known paediatric researcher and author of the Medical Research Handbook, informed that hospitals also started setting up their own ethics committees. In addition to industry sponsored research, the Ministry of Health drew up its own research priority list and application for ethics was linked to application for funding. A lot of the research in the 80s and the 90s were linked to IRPA (Intensification of Research in Priority Areas), which were funded by the Ministry of Science and Technology. "Researchers were self-driven, there was no national force and local support then," Dr Amar adds. Researchers employed Research Assistants using money from these grants. These staff were temporary, it was difficult to build a solid foundation .

In 1997, the idea of a Clinical Research Centre (CRC) was conceived and by August 2000, the CRC was operational as the clinical research arm for the Ministry of Health. CRC's mission is to improve patients' outcomes through quality and ethical clinical research. Dr Zaki Abdul Morad who took on the challenge as CRC's first director, promoted CRC as a provider of integrated clinical research services and encouraged industry and research organisations to partner it.[6]

The country's landmark was the release of two guidelines in 1999 - the Malaysian guideline for Good Clinical Practice (GCP) and the guidelines for application to conduct clinical trials. These were initiatives of the National Committee for Clinical Research, which was formed in 1997 and chaired by the Director-General of Health. The members of this committee are from the Ministry of Health (MOH), industry, academia and societies. The GCP guideline, which is currently in its third edition, details how drug-related trials in Malaysia should be conducted in line with international ethical and scientific standards.[7] The guideline for application to conduct trials, which is currently is in its fifth edition, is now known as the guidelines for application of clinical trial import licence and clinical trial exemption in Malaysia. This guidelines reflects Malaysia's regulatory framework for the country.

> ***"Not every doctor should be doing research, but every doctor should be using research findings."***
>
> **Dr Amar Singh**
> author of the Medical Research Handbook

A New Century (2000-2010)

Robust regulatory, efficient ethical processes, better infrastructure, increase in the number of investigators and the start of a nationwide network. But inadequate support for investigators and sites.

In year 2000, all clinicians who plan to conduct research were required to undergo approved GCP training and by year 2005, almost 800 people were trained in GCP.[8] Many were clinicians from the public hospitals. With proper GCP and regulation, pharmaceutical companies started having more confidence, and more trials poured in. Within a year, the number of phase III trials almost doubled. There were also an increase in the number of phase II trials. The dream to have a CRC in each of the major public tertiary hospitals in the country was continued by Dr Zaki's

successor, Dr Lim Teck Onn, who also led the set up of the One-Stop Centre and the National Medical Research Register. By the year 2010, there were 20 CRCs. The CRCs are the point of contact to the general and district hospitals as well as the health clinics within its vicinity. Researchers no longer need to work in isolation and the conduct of trials became better organised and coordinated. Nevertheless, for many clinicians, clinical trial was still a foreign word, especially in the district hospitals and clinics. An investigator we talked to mentioned that although he has been doing research since the 90s, his first experience in trials only came when he moved to a bigger hospital.

The Ministry of Health's Medical and Research Ethics Commitee (MREC) which was established in 2002 was previously two separate committees in the IMR. With its own secretariat, and later with the introduction of online application through the National Medical Research Register, the process of getting approval from MREC became faster and centralised. Although the MREC is the Institutional Review Board for research involving human subjects by the Ministry's staff or in its facility, it also reviews submissions of investigators from institutions without an ethics committee. Our regulatory process also became equally as efficient. The launch of the National Medical Research Register (NMRR) in 2007 was a breakthrough. It became the portal for researchers to register their research. From May 2007 to December 2009, over 1,000 research proposals were uploaded. The NMRR was the world's online pioneer for linking research proposal registration to ethical review and research grant applications.[9] By now, ethics approval takes between 1 and 3 months and regulatory approval within 2 months; this is comparable to other countries like Hong Kong and Taiwan.[10]

Dr Amar commented that although industry sponsored research is well regulated in Malaysia, 40% of research initiated by researchers in the Ministry of Health were not registered with the NMRR. He called for more oversight and support for investigator-initiated research.

In 2007, the concept of Malaysia as a regional Clinical Trials hub was coined.[8] It was the year when the network of CRCs was launched as the One-Stop-Centre. The trial sponsors had the better option to access investigators through the CRCs. By that time, Malaysia was placed as a Tier Three country for clinical trials, which means our services are high in quality and low in cost, the same as India, China, Indonesia, the Philippines and Thailand.[8]

Unlike the early days, clinicians had better infrastructure and equipments to conduct trials. Our regulatory and ethical processes significantly improved and training for GCP became well structured. "But time waits for no researcher, even one heavily burdened by clinical work", laments our researchers. Clinical trials are not done by individuals, and a capable and keen study team is integral to the process. One researcher mentioned that skilled study coordinators are still hard to find, and more people need to be trained. He also added that some research sites were organised better than others.

Vision 2020 and the Next Generation (2010 till present)

Orchestrating Malaysia's talents, resources and capacities as a national agenda in the aim to make Malaysia a global contender for clinical trials.

In 2010, 1,000 key stakeholders got together for 2 months to identify the key areas in healthcare that can contribute to the country's development. Clinical research made the cut and Clinical Research Malaysia (CRM) was born to create a supportive ecosystem for the industry.[11] The official launch was in July 2011, and Health Minister, Dato' Sri Liow Tiong Lai in his speech depicted CRM as the single, information and referral entry point to our extensive network of 341 hospitals and hundreds of clinical trial sites.[12] He also mentioned that CRM will concentrate on improving Malaysia's position in the global contract research industry. With CRM's corporatisation in 2012, things began to be in place. In addition to be the point of contact, CRM will assist with the administration and management of the trials. Importantly, CRM brings transparent and efficient trial budget management. The aim is to reduce paperwork to resuscitate research. One of the more challenging role for CRM is creating a team of expert professionals who can work with the investigator to ensure high quality and unwavering ethics.

Like the many milestones before it, CRM is positioned to bring significant changes to the clinical trials ecosystem.

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Snapshot of MOH Milestones in Clinical Research

1982 • IMR established its Clinical Research Centre.

1992 • The first patient registry, National Renal Registry, was established. As of 2011, there were 28 patient registries.

1997 • The steering committee for Clinical Research was formed. In 2000, it became the National Committee for Clinical Research.

1999 • The release of the first edition of the Malaysian Guidelines for Good Clinical Practice (GCP). The GCP guideline is currently in its third edition.

- The release of the first edition of the Guidelines for application to conduct clinical trials in Malaysia. This later became the Guidelines for application for clinical trial import license and clinical trials exemption. It is currently in its fifth edition.

2000 • The set up of Ministry of Health's Clinical Research Centre (CRC).

- Clinical researchers required to have GCP and adhere strictly to the Malaysian Guidelines for GCP.

2001 • Clinical research included as a research priority area in the 8th Malaysia Plan.

2002 • The Ministry of Health's Medical Research Ethics Committee was established.

2003 • The National Institutes of Health (NIH), a network of MOH's research institutes, was formed. IMR and CRC became part of the NIH.

2006 • RM90 million allocation for health research under the 9th Malaysia Plan.

2006 • Contract research identified as one of the targeted industries under Malaysia's 3rd Industrial Master Plan.

2007 • The launch of the network of CRCs as a "One-Stop Centre". By 2012, there were 27 CRCs nationwide.

• The launch of the National Medical Research Register as an online portal for the registration of trials.

• Ethics committees must be registered with the National Pharmaceutical Control Bureau (NPCB).

• The First National Conference for Clinical Research was held.

• All MOH research must be registered in NMRR and go through MREC.

• All publications and presentation from MOH research must be approved by the Director-General of Health.

2009 • The National Healthcare Statistics Initiative (NHSI) was set up to collect data on the services, facilities, workforce and medical technologies available in the country.

• The Guidelines for stem cell research and therapy was released. The Director-General of Health released a circular on the application to conduct such research in 2011.

2010 • The Guidelines for Good Clinical Practice Inspection was released.

• All Clinical Trials requiring CTIL/CTX in public, private or academic institutions must be registered with the National Medical Research Register.

• Clinical investigators must undergo GCP courses recognised by the National Committee for Clinical Research.

• Contract research included in the National Key Economic Area for healthcare. Clinical Research Malaysia was launched by the Minister of Health in 2011.

2011 • The Director-General of Health released a circular on the transportation of blood samples overseas for pharmacogenetic/ pharmacogenomic analysis relevant to the clinical trials conducted.

• The establishment of State Research Committees.

2012 • The National Pharmaceutical Control Bureau must be notified of any Bioavailability and Bioequivalence studies.

• Clinical Research Malaysia was corporatised to become an enabler and facilitator for contract research in Malaysia.

• The Minister of Health announced the construction of a RM35 million clinical research centre in Sarawak.

• Hospital fee exemption for subjects involved in investigator-initiated trials.

2013 • Director-General of Health's circular on Clinical Research Malaysia as payee for the 15% administration fee of the trial budget.

It's in Their Blood:
• Clinical Trials in Public Universities

EVENTS WE LIKE

JUN 2013

4th Annual Clinical Trials Asia Summit 2013

Date: June 7
Venue: Mumbai, India

Examines the current issues faced in clinical trials operations, addressing the risks, timeline and budget stipulations, while effectively tackling key challenges in overcoming trials agreement and site contract arbitration problems.

http://event.ayojak.com/event/4th-annual-clinical-trials-asia-summit-2013

SEPT 2013

4th Annual Executing Global Clinical Trials Conference

Date: September 18
Venue: Boston, United States of America

Covers solutions to the current barriers and challenges in planning and executing successful global clinical trials and in particular, how to reduce the complexities of them.

http://theconferenceforum.org/conferences/executing-global-clinical-trials/overview/

Biosimilars Asia Congress 2013

Date: September 24-25
Venue: Singapore

Features case studies of the opportunities and challenges in clinical trials including implications for clinical development and patient safety.

http://www.biosimilarsasia-congress1.com/

NOV 2013

6th Clinical Trials Conference on Alzheimer's Disease 2013

Date: November 14-16
Venue: San Diego, California, United States of America

The future of clinical trials may lie in the development of combination therapies of two or more drugs. This conference highlights the latest on trying to get these trials off the ground.

http://www.ctad.fr/

FEB 2014

4th Annual Oncology Clinical Trials 2014

Date: February
Venue: San Francisco, California, United States of America

Brings together Senior Vice Presidents, Chief Clinical Officers, global heads, Vice Presidents, directors, heads, managers within pharmaceutical companies and oncology-focused institutions and organisations responsible for clinical trials, clinical research and development, medical affairs, clinical operations, biomarkers, drug development and research and imaging.

http://www.clocate.com/conference/4th-Annual-Oncology-Clinical-Trials-2014/33435/

MAY 2014

Annual Pediatric Clinical Trials Conference 2014

Date: May 7-9
Venue: Philadelphia, United States of America

Addresses global regulatory pathways for overcoming operational challenges to conduct effective paediatric trials.

http://www.zapaday.com/event/363951/2/Annual+Pediatric+Clinical+Trials+Conference.html

Which take longer to be published?
Industry-sponsored trials or trials funded by government or non-profit organisations?

Find your answer in
Time to publication among competed clinical trials, JAMA Intern Med. 2013

WANTED

MENTORS & MENTEES

Malaysian **PROTEGES** 2013

PReparing **O**utstanding Clinical Research **T**alents by **EnG**aging **E**minent Malaysian **S**cientists

Details in the next issue

IT'S NATIONWIDE

Completed
Central Region
Dates: 13 April & 18 May 2013
Venue: Kuala Lumpur

Coming Soon
Northern Region
Dates:15 & 29 June 2013
Venue: Pulau Pinang