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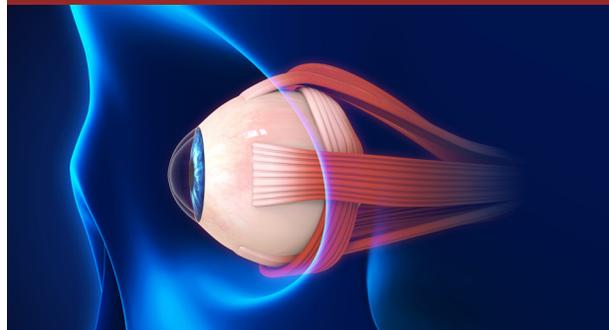


Lee Kong Chian School of Medicine's First EMBO Young Investigator Award Recipient



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The Collaborative Ocular Tuberculosis Study (COTS)



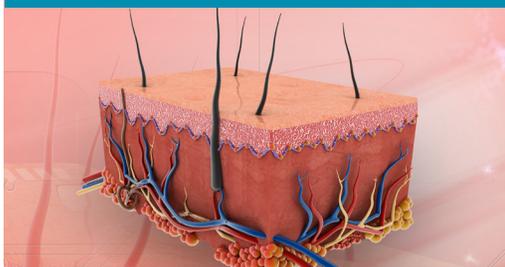
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Helping Monogenic Diabetic Patients with MODY Registry



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Non-Invasive Skin Imaging for Real-Time In Situ 3D Analysis and A Novel Treatment For Hypohidrosis (Inability To Sweat)



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- Tuberculosis or Sarcoidosis: Opposite Ends of The Same Disease Spectrum? – An Ophthalmologist's Perspective
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Congratulations to the following Awardees of the NHG-NTU Clinician-Scientist Fellowship (CSF)!

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The Collaborative Ocular Tuberculosis Study (COTS)

A study to describe the epidemiology of 962 patients diagnosed with tubercular uveitis and the current practices in 25 multinational participating centres.

Tuberculosis (TB) has been a major infectious disease threat since the 1990s. International efforts led by the World Health Organisation (WHO) have been successful by some measures. However, there have been several unresolved limitations including deficiencies in case detection, the resurgence of drug-resistant TB5, and reservoirs of infection in neglected populations. This has prompted a call for international data to facilitate improved diagnosis and management of TB to augment a realignment of healthcare priorities from passive case-finding to active case-finding to eliminate the pool of TB in the population.

Extrapulmonary TB accounts for 15% of the health burden of TB, and increases to 50% in the subpopulation of patients with Human Immunodeficiency Virus (HIV) co-infection. Ocular involvement most often manifests as uveitis, and has been reported in up to one fifth of patients with culture-proven TB along with significant ocular morbidity and visual loss. It may be initially asymptomatic in most patients and can be the first presentation of TB infection with patients seldom having features of manifest systemic TB. However, despite progress in coordinated efforts to address pulmonary TB, the diagnosis and management of TB uveitis remain controversial due to a lack of robust data to substantiate evidence-based guidelines.

The difficulty in the diagnosis of ocular TB infection is partially contributed by its myriad of possible manifestations to affect any tissue in the eye. This is compounded by the need for cautious interpretation of currently available investigations due to limitations in sensitivity and specificity, even with technologies such as the polymerase chain reaction (PCR). The diagnostic uncertainty in TB uveitis leads to delay in targeted therapy and poorer treatment outcomes. This is compounded by unstandardised diagnostic and treatment practices which complicate the interpretation of clinical trials. An explanatory retrospective cohort study of clinical practice at 25 global centres of diverse geographical origin seeks to analyse demographic factors affecting treatment outcomes and describe the current practices in TB uveitis through an international collaboration.

This study involved patients diagnosed with TB uveitis between January 2004 and December 2014, with a minimum follow-up of 1 year. **A novel data entry platform was conceived to address the heterogeneous nature of this disease.** The encrypted web-based platform was programmed as a smart form that provided users with explanations and prompts for questions, and re-enforced information such as inclusion criteria and treatment failure definitions used (above). The form omitted patient identifiers and also standardised data entry, minimising data processing and associated transcript errors. Trivial data entry errors from open-ended entries were manually corrected through transformations in SPSS. Variables for which data was not entered were treated as missing values in that patient for statistical analysis.

962 patients had TB uveitis with a mean age of 41.3 (range 4-90), and a predominance of males (52.6%, n=506/962) and Asian ethnicity (74.4%, n=690/927). Predominantly posterior distribution of uveitis (34.8%, n=326/938) was found, often with features of granulomatous-type of inflammation (50.7%, 372/734). Use of treatment in these patients include no ATT/Steroid (6.18%, 59/954), Steroid only (9.9%, 94/954), ATT only (10.1%, 96/954), and both Steroid and ATT (73.9%, 705/954).

Ethnicity ($X^2=19.860$, $p<0.001$), geographical region ($X^2=21.768$, $p=0.010$), and immigrant status ($X^2=4.865$, $p=0.027$) were significantly associated with poorer survival outcome. Use of Anti-tubercular therapy (ATT) was not associated with improved survival outcome ($X^2=0.182$, $p=0.798$).

The apparent lack of improvement in survival outcomes with ATT use in these patients with TB uveitis highlights diagnostic enigma that needs to be addressed urgently. Further prospective studies are required to assess the pathogenesis and management of the varied ocular manifestations of TB uveitis.



Contributed By:
**Adjunct Assistant Professor
Rupesh Agrawal**
Consultant Ophthalmologist



Dr Dinesh Gunasekaran
House Officer

Department of Ophthalmology
Tan Tock Seng Hospital

Results of NMRC Talent Development Awards and Grants

Name	Institution	Project Title	NMRC Grant / Award
Assistant Professor Tey Hong Liang	National Skin Centre	Three-Dimensional Imaging In Ex Vivo Skin and Non-Invasive Skin Imaging: Novel Clinical Applications In Skin Cancers and Hypohidrotic Sweat Disorders	Clinician Scientist Award-Investigator Category (CSA-Inv)
Dr Yew Yik Weng	National Skin Centre	Novel Device for Transdermal Delivery of Triamcinolone in the Treatment of Nail Psoriasis: A Randomized Intra-Patient Left-to-Right Study.	Clinician Scientist - Individual Research Grant - New Investigator Grant (CS-IRG-NIG)
Dr Alvin Tan Wai Kit	Tan Tock Seng Hospital	Interactions between Insulin Resistance, Osteocalcin and Skeletal Muscle in Older Chinese Males with Type 2 Diabetes Mellitus	NMRC Research Training Fellowship (RTF)
Professor Chong Siow Ann	Institute of Mental Health	A Nationwide Knowledge, Attitudes and Practice (KAP) Survey on Diabetes in Singapore's General Population	Health Services Research Grant (HSRG)
Associate Professor Angela Chow Li Ping	Tan Tock Seng Hospital	Understanding the Psychosocial, Cultural, and Systemic Determinants of Antibiotic Use and Utilizing a Multilevel Approach to Address Inappropriate Antibiotic Use	Health Services Research Grant (HSRG)

DID YOU KNOW?

The M.D.-Ph.D. Double Agent

Do you know the rewards and challenges of a physician-scientist?

Click [here](#) to read about Jessica W. Tsai's experience.

Congratulations to the following Awardees of the NHG-NTU Clinician-Scientist Fellowship (CSF)!



Dr Sabrina Wong*
Consultant Family Physician
Clinical Services
NHG Polyclinics



Dr Chan Lai Gwen
Consultant
Department of Psychological Medicine
Tan Tock Seng Hospital

For more information, please visit www.research.nhg.com.sg (Research Career Development → Schemes for Doctors)

*Also an Awardee of the NMRC Research Training Fellowship (RTF)
Please click [here](#) to find out more about the NMRC RTF

GOOD TO READ!

Effectiveness of Telemedicine for Distant Wound Care Advice towards Patient Outcomes: Systematic Review and Meta-Analysis

Find out more on the systematic review and meta-analysis conducted to evaluate whether the use of telemedicine for distant wound care advice was effective in improving wound outcomes.

Click [here](#) to find out now!

MODY Registry: Reaching-Out To People With Monogenic Diabetes

A group of physicians, nurses, scientists and IT-specialists from Khoo Teck Puat Hospital (KTPH) and Tan Tock Seng Hospital (TTSH) had started a pilot registry for monogenic diabetes (https://www.ktph.com.sg/cru/section_page/516).

Also known as Maturity-Onset Diabetes of the Young (MODY), monogenic diabetes is estimated to afflict 2,500 to 5,000 people in Singapore. MODY describes a subset of individuals with diabetes caused by a single gene abnormality (leading to impaired insulin production), and often remains undiagnosed until adulthood. Clinically, people with MODY looks similar to those with Type 1 or Type 2 diabetes (the more common varieties) and genetic testing is often the only means to confirm the diagnosis of MODY.

An accurate diagnosis of MODY is important because these people may require specific anti-diabetic treatment different from Type 1 and Type 2 diabetes. Moreover, it is increasingly recognised that different subtype of MODY requires different diabetes management plan.

Therefore, funded by the Alexandra Health Fund Ltd, we setup the pilot MODY registry with the following aims:

1. To identify individuals with MODY and to perform genetic testing for this group of individuals.
2. To facilitate optimisation of treatment by their care-provider for individuals with confirmed genetic diagnoses.
3. To provide MODY-related counselling to affected individuals and their family members.
4. To provide a platform for gathering longitudinal information to better understand and treat monogenic diabetes.

The KTPH-NHG MODY registry was established in April 2017, with data from 35 patients on the registry. The group is also collaborating with KK Women's and Children's Hospital (KKH), Genome Institute of Singapore (GIS), and the Institute of Molecular and Cell Biology (IMCB) with the hope of serving people with MODY better.



Figure 1. MODY Registry Study Team. 1st row, from left: (From KTPH) A/Prof Subramaniam Tavintharan, A/Prof Lim Su Chi, A/Prof Sum Chee Fang, Mr Dave Lee, Dr Ang Su Fen, Ms Jessie Fong, Ms Clara Tan. 2nd row, from left: Dr Ester Yeoh, Dr Tan Hwee Huan, Dr Than Win. (From TTSH) Dr Winston Kon, APN Lian Xia. Other collaborators not pictured: A/Prof Fabian Yap (KKH), Dr Liu Jian Jun (GIS), Dr Rajkumar Dorajoo (GIS), Dr Adrian Teo (IMCB).

Contributed By:
A/Prof Lim Su Chi
Clinical Director,
Clinical Research Unit
Khoo Teck Puat Hospital

The CSPP Journey

I am currently a Family Physician at the Toa Payoh Polyclinic. After completing my Master of Medicine (Family Medicine) in 2014, I became actively involved in undergraduate and post-graduate Family Medicine teaching.

I am also interested in primary care research but I did not have any formal research training. As I was looking for a programme that would provide basic research training, I got to know of the NHG Clinician-Scientist Preparatory Programme (CSPP) as I was starting my family medicine fellowship training.

I have benefited significantly from the CSPP - **the structured training exposed me to areas such as research ethics, research methodology, study conduct and data analysis.** These courses provided useful knowledge that I could apply in my

research project, which studied the effectiveness of pre-consultation medication reconciliation service in reducing unintentional medication discrepancies in primary care. The project funding by CSPP also contributed to the successful conduct and completion of the project.

In addition, my mentor for the programme, Prof Doris Young, who had been very generous in giving sound advice, critique and sharing of past experiences had inspired me to further pursue research. These components of the CSPP, together with my hardworking team members, have equipped me with the essential research knowledge and networks early in my career.

I have always believed that **research is the key to better clinical and primary care.** CSPP has given me the impetus and collaboration platform for further

training and involvement in primary care research. I hope to be able to motivate my colleagues and juniors to embark on this journey as well.



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Assistant Director
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National Healthcare Group Polyclinics
CSPP FY16 Awardee

Deconstructing the Complex Relationship Between Predictors, Mediators and Outcome Data in Mental Health Research

Mediation analysis is a fast growing field in epidemiology that helps researchers to deconstruct the effect of an exposure on an outcome into number of pathways via third explanatory variables known as mediators which in turn influence an outcome. The application of mediation analysis using structural equation modeling framework may provide a greater insight into the nature of treatment effects of our existing intervention programmes and explore the complex relationship between predictors, mediators and outcome data in mental health research.

I was delighted when the NHG Research Support Scheme provided me an opportunity to study the usefulness of this statistical model using two existing databases (clinical database from the Early Psychosis Intervention Programme (EPIP) and that of the Well-being of Singapore Elderly (WiSE) study).

In the first study, we examined how socio-demographic factors, modifiable health factors including vascular risk factors (heart problem, stroke, transient ischaemic attack, diabetes, and hypertension), depression, and lifestyle risk factors (physical activity, social contact and loneliness) influence each other, and subsequently, lead to dementia using data from WiSE study¹. **We found that physical activity and more frequent contact with friends played an important role as mediators in this relationship and suggests that older adults who had higher risk of dementia were less likely to have dementia if**

they were physically active and had frequent contact with friends. The results also found that the relationship between occupation and dementia was mediated by physical activity which suggests that engagement in intellectual, social and physical activities (via occupational attainment and higher level of physical activity) may stimulate the brain and result in more efficient use of brain networks.

In the second study, we explored the nature of symptom trajectories and its impact on functioning among patients with first episode psychosis (FEP) over a 2-year follow-up period using a latent class growth analysis². Our results suggest that there is **evidence of two distinct trajectories (early response and stable trajectory and delayed response trajectory) for positive symptoms and four distinct trajectories (early response and stable trajectory, early response and relapse trajectory, slower response and no response trajectory and delayed response trajectory) for negative and general psychopathology symptoms among patients with FEP.** As compared to early response and stable trajectory, patients belonging to other trajectories either in negative, positive and general psychopathology symptoms were more likely to have deterioration in functioning over time. This study also suggests that there are small groups of patients who may be at a higher risk of deteriorating symptom severity than others. Hence, future studies are needed to explore treatment strategies that are tailored to the

specific needs of patients who do not benefit sufficiently from standard treatment which may include extending the treatment follow up.

References:

1. Abdin E, Chong SA, Peh CX, Vaingankar JA, Chua BY, Verma S, Jeyagurunathan A, Shafie S, Subramaniam M. [The mediational role of physical activity, social contact and stroke on the association between age, education, employment and dementia in an Asian older adult population.](#) *BMC Psychiatry*. 2017 Mar 20;17(1):98. doi: 10.1186/s12888-017-1272-8.
2. Abdin E, Chong SA, Vaingankar JA, Peh CX, Poon LY, Rao S, Verma S, Subramaniam M. [Trajectories of positive, negative and general psychopathology symptoms in first episode psychosis and their relationship with functioning over a 2-year follow-up period.](#) *PLoS One*. 2017 Nov2;12(11):e0187141. doi: 10.1371/journal.pone.0187141. eCollection 2017.



Contributed By:

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Lee Kong Chian School of Medicine's First EMBO Young Investigator Award Recipient

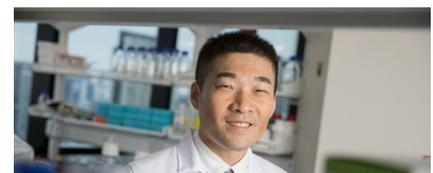
On October 25, 2017, Nanyang Assistant Professor Luo Dahai added another first for both Lee Kong Chian School of Medicine (LKCMedicine) and Nanyang Technological University, Singapore, when he received the prestigious EMBO Young Investigator Award. He is among 28 researchers under the age of 40 from 11 countries who were recognised by Europe's foremost life sciences body for their exceptional research and scientific potential. Asst Prof Luo is one of four EMBO Young Investigators from Asia and he joins a network of 47 current and 417 past Young Investigators who represent some of the best up-and-coming group leaders in the life sciences in Europe and beyond.

Asst Prof Luo was recognised for his contributions to RNA viruses and host defence, in particular his recent breakthrough about the structure of NS2B-NS3, two key virus replication proteins, found in common flaviviruses such

as dengue, Zika and West Nile. Leading a team of researchers from LKCMedicine, NTU's School of Biological Sciences, NTU Institute for Structural Biology and A*Star's Experimental Therapeutics Centre (ETC), Asst Prof Luo found that the established practice of using artificial linkers, or chemical bonds, to study these proteins actually reduces the accuracy of the data gathered, hampering the drug discovery process.

By successfully combining NS2B with NS3 without a linker, the team was able to precisely record the proteins' native state, shedding light on their exact function, structure and suitability for structure-based drug development by identifying unique target regions that potential drugs could target to stop the replication process. Since this breakthrough in 2016, the team has proceeded to further proof-of-concept studies for a structure-based antiviral design that targets proteins needed for the Zika and

dengue virus to reproduce. They are also working with scientists from ETC to develop potential drugs that can disrupt the protein and stop the virus from replicating.



On his award, 34-year-old Asst Prof Luo said, "I am thrilled to hear the news from EMBO. It is not only recognition of the work I and my research team has done, but also the favourable environment here at NTU. It is an encouragement to continue with good science."

Contributed By:

The Lee Kong Chian School of Medicine

Non-Invasive Skin Imaging for Real-Time In Situ 3D Analysis and A Novel Treatment For Hypohidrosis (Inability To Sweat)

The traditional method of skin investigation involves the use of excised skin specimens and 2-dimensional analysis. There are still many skin diseases which we do not understand and cannot treat. Our team advocates an approach to study certain disease processes real-time in patients' skin in situ and to leverage on 3D technologies for analysis, in order to obtain new insights into disease pathologies and treatments.

Heat injuries and heat stroke-induced deaths are not uncommon occurrences worldwide and they are of particular relevance to hot and humid countries like Singapore. We have previously found that hypohidrosis, or the inability to sweat, is a prominent factor in our soldiers who developed heat injuries.¹ To address our deficiencies in diagnosing and treating hypohidrosis, we leverage

on non-invasive skin imaging, using high-definition Optical Coherence Tomography in this project.²

One type of hypohidrosis is known as miliaria profunda. By imaging the skin lesions in patients' skin in situ real-time, we identified features that are not seen in traditional histology. Use of 3D technology facilitates the ease and speed of identification of these features, such that the process can be practically implemented in the clinics in future. **With the new understanding of the pathogenesis of miliaria profunda, we were able to institute a novel treatment using systemic retinoids. Non-invasive skin imaging is currently being incorporated as a routine bedside diagnostic tool for patients presenting with hypohidrosis, and systemic retinoids is now used for the treatment of miliaria profunda in our centre.**

References:

1. Lim JHL, Kok WL, Chong WS, Tey HL. Prevalence of hypohidrosis in healthy individuals who developed exertional heat injury: a prospective open cohort study. *Dermatology*. 2016;232(1):50-6.
2. Cao T, Tey HL. High-definition optical coherence tomography – an aid to clinical practice and research in Dermatology. *Journal der Deutschen Dermatologischen Gesellschaft*. 2015;13(9):886-90.

Contributed By:

Asst Prof Tey Hong Liang
Head, Research and Senior Consultant
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National Skin Centre
SHBC 2017 Clinician Investigator Award (Gold) Awardee



Tuberculosis or Sarcoidosis: Opposite Ends of The Same Disease Spectrum? – An Ophthalmologist's Perspective

Tuberculosis (TB) and sarcoidosis are chronic, multi-systemic, granulomatous diseases which are closely linked in their pathogenesis and clinical manifestations. In fact, current overwhelming evidence suggests that TB and sarcoidosis may be manifestations of the same disease spectrum.

Epidemiological studies show that previous contact history of TB and populations with higher prevalence of TB were closely associated with sarcoidosis and that both diseases may coexist in the same patient. Clinically, they share similar features – in the setting of ophthalmology, both present as 'great imitator' of many uveitic conditions; whereas systemically, they may present with non-specific constitutional, pulmonary or extrapulmonary symptoms. Immunologically, they incite similar responses from the body – such as the presence of increased levels of pro-inflammatory response to particular mycobacterial antigens and genomes.

Therefore, in our review, we postulated that TB and sarcoidosis can represent a spectrum of the same disease. While sarcoidosis can be caused by non-infectious agents, it can also be a result of *Mycobacterium tuberculosis* (MTB) infection in a host with a strong cellular immunological response. The difference in the immune response of the host

may lead to varying degrees of presentations. Hence, a classification system for variants of TB and sarcoidosis has been proposed (Figure 1) that may be useful in the management of patients.

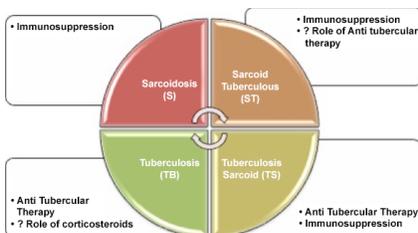


Figure 1: 'Pure' sarcoidosis (S); 'Pure' tuberculosis (TB); Predominantly sarcoidosis with tuberculous features (ST); Predominantly tuberculous with sarcoid features (TS)

In pure sarcoidosis or TB, current management guidelines (i.e. immunosuppressants for S and anti-TB medications for TB), can continue to be undertaken. As it has been postulated that the management of sarcoidosis with steroids and immunosuppressants may reactivate TB in the absence of concurrent anti-TB medications, those with features of both TB and sarcoidosis (i.e. ST or TS) can be treated with a combination therapy, with

both immunosuppressants and anti-TB medications, so as to avoid reactivation or under treatment of one or another.

Therefore, it is important to make an appropriate diagnosis, with the aid of current available laboratory and radiological investigations, as this will ultimately affect the management of the patient. However, before further conclusions can be drawn with any certainty, more research needs to be done to affirm this link between the two diseases.

Further information can be found in "[Tuberculosis or Sarcoidosis: Opposite ends of the same disease spectrum – An Ophthalmologist Perspective](#)" *Tuberculosis* May 2016

Contributed By:

Dr Kee Ae Ra
Medical Officer

**Adjunct Assistant Professor
Rupesh Agrawal**
Consultant Ophthalmologist

Department of Ophthalmology
Tan Tock Seng Hospital



Understanding Causality

I am currently a PhD student at King's College London studying towards a doctorate in Biostatistics. My current work focus on developing methods that allow one to **establish whether a causal relationship exist between processes involved in delivering a treatment and the desired outcome, known more commonly as process evaluation.**

My interest in causal inference started from thinking about the adage that "correlation does not imply causation" and I thought aloud to myself, "What then implies causation?". This innocent question turns out to be a highly important and

hotly debated topic in science. The importance stems from the need to know how things work and this is especially true in many areas of medicine. The difficulty however lies in determining which of the many elements in an uncontrolled and complex environment is responsible for causing the effect of interest.

I hope that when I return, I can apply many of the lessons learned to help in disentangling association from causation and in so doing, bring about a better understanding of the different aspects of our healthcare system through my work at Health Services & Outcomes Research.

Contributed By:

Mr Li Ruijie
Principal Research Analyst
Health Services & Outcomes Research (HSOR)
National Healthcare Group
NMRC Research Training
Fellowship (RTF) Awardee

Please click [here](#) to find out more about the NMRC RTF



My PhD Journey as a Clinician

In order to formalise and further my research training with good supervision and mentoring under international renowned researchers, I started my PhD studies with Lee Kong Chian Medical School (LKCMedicine), Nanyang Technological University, Singapore in January 2017.

My PhD research project aims to study disease prevalence and risk factors association of adult atopic eczema in a population cohort. My supervisors are Prof John Chambers from LKCMedicine and Prof Steven Thng from National Skin Centre, Singapore.

This area of research has been generating interests and attention as there have been increasing evidence to suggest **association of several co-morbidities with adult atopic**

eczema, including metabolic syndrome and other atopic conditions.

So far, my experience as an LKCMedicine PhD student has really been very positive with strong support from fellow PhD students, administrative support and the teaching faculty. There have been prompt assistance and good flexibility to help students achieve their goals and training. Via my interactions with other PhD students in other fields of research, I could better appreciate and empathise the rewards and challenges of a basic science research scientist and how the outcomes of their research could potentially be translated into actual clinical care.

My superiors at work have also been very supportive and encouraging of my PhD studies so

far making it possible and easier for me to juggle my time for clinical and work duties on top of my PhD studies.

I hope to consolidate my research skills, network with established research members, publish important scientific results on eczema epidemiology research. Given a chance, I would like to further my career as a Clinician-Scientist in the area of dermatology and epidemiology research.



Contributed By:
Dr Yew Yik Weng
Consultant
Dermatology
National Skin Centre

Training Calendar

SN	Date	Training Programme
1	Monthly	Good Clinical Practice (Online)
2	Monthly	(PCR100) Study Start-Up: Budgeting, Case Report Form Design and Database Design
3	Monthly	(PCR200) Study Conduct I: Subject Recruitment and Informed Consent
4	Monthly	(PCR300) Study Conduct II : Documentation, Safety Reporting and Investigational Products
5	Monthly	(PCR400) Monitoring, Audits and Inspections
6	5 Mar 18	Intellectual Property
7	2 Feb 18	2nd Run: Excel for Research Workshop
8	22 Mar 18	2nd Run: Basic SPSS Workshop

*Dates are subject to changes without prior notice.

For registration and full details on courses by:

~ NHG Research & Development Office (RDO) (Courses 1 - 6), please visit www.research.nhg.com.sg (Training & Education → Register for Courses and Other Events)

~ TTSH CRIO (Courses 7 & 8), please contact Ms Siti Aisha Binte Jaffar (Siti_Aisha_JAFFAR@ttsh.com.sg)

Qualité (Issue 29, Jan 2018)

Education to facilitate high standards of research conduct

1. Outsourcing Study-Related Functions to External Service Providers - Tips for Study Conduct

Find out how Principal Investigators (PIs) of research studies should comply with applicable research policies and regulatory requirements when engaging external service providers to perform study-related functions.

Click [HERE](#) to read on the responsibilities of the PIs and the documentation required.

2. Updates to the Reporting of Expected Serious Adverse Events (SAE) [According to the new requirement of the Human Biomedical Research Act (HBRA)]

Click [HERE](#) to find out more on the reportable events and the submission process to DSRB.

FMHS 2018

Frontiers in Mental Health Symposium

Advancing Research in Depression and Psychosis

Keynote Speaker

Sir Philip Campbell
Editor-in-Chief of Nature, and Nature Research



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