Clinical trials evolving as they advance treatment

Singapore has set its sights on becoming a regional centre for clinical trials as these will give Singaporeans early access to new treatments and drugs.

In view of World Clinical Trials Day last Friday, Clara Chong looks at three different trials and explores how the nature of clinical trials has changed over the years.

World Clinical Trials Day was started to recognise the work done by Scottish doctor James Lind on May 20, 1747, when he started what is often considered the first randomised clinical trial aboard a ship.

Clinical trials, which are the bedrock of modern medicine, have changed significantly over the years.

"Trials need not involve drug interventions. For example, trials can involve the follow-up of groups of individuals with specific characteristics to better understand the factors which contribute to development of disease," Dr Sue-Anne Toh, an adjunct associate professor of medicine at the National University of Singapore, told The Straits Times in an exclusive interview.

"From there, we can potentially learn about how we can enhance interventions, whether they be medications or specific lifestyle changes, to alter the course of progression to disease or complications," said Dr Toh, who is also leading some clinical trials on diabetes at the National University Hospital.

Such observational trials likely involve healthy participants too, and are not limited to people with or at risk of disease.

With technology, the manner in which trials can be conducted has also evolved, and they no longer necessarily involve a face-to-face meeting. Instead, they can be conducted via virtual platforms, polls and structured questionnaires, and can be a mix of all these different modes, Dr Toh added.

Finally, a globally connected world has also facilitated multi-centred trials, where participant profiles can come from different geographical locations.

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Diabetes

Study on progression of disease in Asian populations

Dr Sue-Anne Toh, an adjunct associate professor of medicine at the National University of Singapore, and her team conducted one of the world's largest comprehensive scientific studies on the progression to diabetes in Asian populations. The three-year study ended at the start of this year.

Type 2 diabetes is an increasing epidemic in the region, and it is projected that its prevalence in Singapore will double from 7.3 per cent in 1990 to 15 per cent in 2050. The total economic cost of the disease alone is expected to increase by 2.4 fold.

In the West, where there is a higher prevalence of obesity, there is a stronger correlation between weight loss and a reduced risk of developing diabetes. However, this is not necessarily true in the Asian context, Dr Toh said.

"We may be very lean and even underweight and, yet, have diabetes. And there may be certain aspects of biology that are very different in us compared to Caucasians and telling these thin people to lose weight is not helpful, and in fact, can be very demoralising," she said.

"But with this study, we'll have our own local data that is relevant to the Asia-Pacific region, which will help contribute to our understanding of what other factors – be they biological, environmental or lifestyle – also contribute to the progression of diabetes in our population."

The study, called Assessing progression to type-2 diabetes (APT-2D): A prospective cohort study expanded from brite-spot (Bio-bank and registry for stratification and targeted interventions in the spectrum of type 2 diabetes), involved 1,679 Singaporeans with pre-diabetes or normal blood glucose levels.

Dr Sue-Anne Toh says people may be very lean and even underweight and, yet, have diabetes.

It was found that having an impaired ability to secrete insulin was a landmark feature of those with pre-diabetes.

"We know that type 2 diabetes occurs when the body cannot respond well to the actions of insulin ("insulin resistance") and the pancreas cannot make enough insulin to keep glucose levels within normal range. However, the exact contribution of each defect and the timing at which it occurs in the progression of diabetes is incompletely understood, especially in Asians," Dr Toh said.

"Our study has shown that in the Singapore population, those with pre-diabetes have mild insulin resistance but a disproportionately greater inability to produce enough insulin. Our findings provide important insights into the main factors that drive the development of abnormal glucose levels in Asians."

"This suggests that interventions which focus on not overworking the pancreas could be particularly effective in lowering the risk of type 2 diabetes in Asians," Dr Toh added.

A study participant, who wanted to be known only as Ms Tang, was glad that she volunteered. It was through this study that Ms Tang, a manager in her 30s, found out she had pre-diabetes.

She knew of the study via an e-mail that was sent to all employees at her previous workplace.

"It was my first time participating in a clinical trial and the process was generally very smooth," she said.

Ms Tang, a manager in her 30s, found out she had pre-diabetes when she took part in the APT-2D study. She now makes an effort to incorporate some physical activity in her daily routine. ST PHOTO: SYAMIL SAPARI

The study team closely monitored her blood sugar levels once every six months over three years – from 2018 to last year.

"As I am of a healthy weight and generally do not consume too unhealthy food, I did not think that I'd have pre-diabetes," she added.

Ms Tang, who did not lead an active lifestyle in the past, now puts in effort to incorporate some physical activity, such as Zumba classes or brisk walking, into her daily routine in order to keep her glucose levels in check.

Infections

'Trojan horse' may aid fight against antibiotic resistance

Antibiotic resistance in infections such as pneumonia, bloodstream infections and wound or surgical site infections is a common problem.

This is especially since all antibiotics that are currently used to treat these infections belong to the same class and have similar modes of action.

However, the discovery of Cefiderocol, a new antibiotic with a Trojan horse mechanism of action that acts on these infections, has proved to be a game changer, said Associate Professor David Lye, director at the Infectious Disease Research and Training Office in the National Centre for Infectious Diseases (NCID).

A Trojan horse refers to any kind of deception that involves getting a target (the bacteria) to willingly allow an enemy (the antibiotic) into a secure place (the cell of the bacteria).

Cefiderocol acts on the channel that transports potassium across the cell membrane.

Potassium is a salt that is very important to the cell's function.

Cefiderocol enters the bacteria via the potassium channel and kills the bacteria once it is inside, Prof Lye said.

Traditionally, antibiotics destroy the integrity of the bacterial membranes and cause the cells to burst.

However, some of these bacteria soon adopt a unique structure of their outer membrane, preventing certain drugs and antibiotics from entering the cell, resulting in resistance.

A clinical trial on Cefiderocol, aptly named Gamechanger, investigates this new mode of action.

The trial is led by Professor David Paterson, director at The University of Queensland Centre for Clinical Research.

Retiree Ang Hwee Kheng, 55, who was recruited to be part of the trial earlier this month when he was hospitalised as bacteria was detected in his blood, said the trial process has been smooth so far.

Associate Professor David Lye said the discovery of Cefiderocol has proved to be a game changer.

"I wanted to join the trial to contribute to medicine so that better care can be given to others in the future," Mr Ang told The Straits Times in a phone call.

His doctor recommended that he join the trial and Mr Ang did not have any reservations in doing so.

Mr Ang takes the antibiotic via an intravenous drip and does not have to pay for medical tests or antibiotics since they are funded by the trial.

Ongoing study

NURTURE (NUh Repository of TissUe and data for Research in Endocrinology) is the National University Hospital's (NUH) initiative to build a secure biorepository of tissue and health records data for research in the National University Health System (NUHS). This provides resources to NUHS' investigators for diabetes-related studies ranging from genetics and diagnosis to diets/lifestyles and clinical care treatment.

Those who want to be part of the study can call 9072-4185/9071-9782 during office hours or send an e-mail to NUH_nurture@nuhs.edu.sg

Cancer

Turning to philanthropy to test halving dose for patients

Newer cancer drugs have come with increasingly higher costs, making it harder for those who need treatment to gain access to them.

"In Asia, cancer diagnosis can be catastrophic for households who are unable to afford it. Though some of these costs are borne by insurance and the Government, there needs to be a way for these costs to be optimised," said Professor Goh Boon Cher, deputy director of research at the National University Cancer Institute, Singapore.

One way is to relook the dose of the drug given, he added.

In a rush for a drug to get registered, the drug is sometimes given at higher doses in the hope that this will lead to a better outcome.

The same result can actually be obtained with a lower dose, but this option is not tested as the trial may not have been as extensive, Prof Goh said.

One example is epidermal growth factor receptor (EGFR) mutant lung cancer, where a mutation in the gene for EGFR can make it grow too much, leading to cancer.

This particular mutation occurs in more than 40 per cent of tumours in Singaporean lung cancer patients.

The drug to treat this cancer costs about $8,500 a month.

After examining the pharmacology of the drug, Prof Goh and his team started a trial to recruit 60 patients to find out if halving the dose would achieve the same clinical benefits.

However, funding is a stumbling block. Conventionally, trials are funded by pharmaceutical companies, but such a trial would hold little incentive for them, given an erosion of profits should the dose be halved.

"We, hence, turn to philanthropy," Prof Goh said.

"Our trial remains underfunded at this stage but such trials are hugely beneficial to patients – they are able to pay less for the same outcome and potentially experience fewer side effects."

Additionally, patients can take part in more than one trial and there should not be a misconception that the elderly cannot participate in trials, Prof Goh added.

Madam Hee Poh Lian, 83, who has nasopharyngeal cancer, is one example.

Her first clinical trial experience was an immunotherapy trial, which she started after completing a round of chemotherapy treatment. Her second clinical trial was an oral chemotherapy type.

"The process has been very smooth and the staff have been very nice. They calmed me down and always made sure to check on me," said Madam Hee, whose condition has improved after both trials.

Professor Goh Boon Cher (far left), deputy director of research at the National University Cancer Institute, Singapore, and his team started a trial to find out if halving the dose of a drug to treat a type of lung cancer would achieve the same clinical benefits. PHOTO: NATIONAL UNIVERSITY CANCER INSTITUTE, SINGAPORE