# What does it Take to have a Good Experience of Recruitment in Clinical Research: Malaysia

**Introduction**
A staggering number of clinical trials fail to meet recruitment goals, leading to delays, early termination, or inability to draw conclusions at trial completion due to loss of statistical power. It is estimated that roughly 80% of clinical trials fail to meet enrolment timelines and approximately 30% of Phase III study terminations are due to enrolment difficulties[1]. In a separate analysis of more than 100 trials, the data showed that less than a third and half were awarded an extension[2]. The impact of failure to enrol patients and meet with timelines can delay product launch that could translate into huge financial losses for the pharma company.

**Patient Recruitment: Asia vs. Europe & USA**
Traditionally, industry-sponsored research has been conducted in high-income countries in Europe and the US due to their established research infrastructure, and being the birthplace of major pharma companies[3]. However, globalisation has resulted in shifting this research outside these countries by reaching out to Asian countries. The key thing that attracts a pharma company to approach the Asian population is the availability of treatment-naïve patients, which has resulted in speedy recruitment. The large treatment-naïve population including Japan, Malaysia, Thailand and China presents a significant opportunity[4]. One of the barriers to conducting clinical trials in the US and Western Europe is participant recruitment and retention. In the US and Western Europe, racial and ethnic minorities, women and the elderly are often underrepresented in enrolment. One trial for HIV-associated cryptococcal meningitis recognised low US patient enrolment and subsequently added Thailand as a trial site, where it recruited 99 patients in five sites. The trial added an average of four patients per site in Thailand over three months compared with one per site in the United States[5]. Malaysia has a strong research ecosystem in all its healthcare facilities, provided by the Ministry of Health (MoH), Ministry of Education (MoE) and private hospitals. In MoH, the responsible unit for conducting clinical research is the clinical research centre (CRC) which is located at every public hospital. To date, there are 35 CRC distributed in the peninsular and East Malaysia. Under MoH, there are also government health clinics or *'klinik kesihatan'* which support the work of clinical research in Malaysia. Besides the facilities provided by MoH, there are also teaching hospitals under the purview of MoE that are actively conducting clinical research, namely the University Malaya Medical Centre (UMMC), Universiti Kebangsaan Malaysia Medical Centre (UKKMC), Hospital University Sains Malaysia (HUSM) and International Islamic University Malaysia Teaching Hospital (IIUM Teaching Hospital). And last but not least, there are also several private hospitals conducting clinical research and are supported by a private clinic. In 2018 and 2019, there are about 330 trials conducted in Malaysia in all healthcare facilities with 235 of these trials being conducted in MoH facilities, and the remaining trials were conducted at MoE and private facilities.

**Clinical Research Malaysia (CRM)**
CRM is a non-profit company wholly owned by the Ministry of Health. CRM was established in June 2012 to position Malaysia as a preferred global destination for research and to function as an enabler and facilitator to the industry and medical fraternity for the conduct of clinical trials. CRM plays an important role in improving the local ecosystem to support growth in industry-sponsored research, facilitate the needs and requirements of industry players, grow the pool of capable investigators, support staff and trial sites and improve their capabilities and capacities to conduct this research. CRM is committed to work on three important key strategies; quality, speed and reliability, to ensure satisfaction of relevant stakeholders. With the controversial challenges in patient recruitment globally, CRM has set a key performance index (KPI) to support the recruitment performance of the trials supported by CRM. One of the parameters that we are monitoring is on recruitment achievement for all sites that completed recruitment and we are going to discuss this parameter (result from year 2018 and year 2019) in this article.

## Methods

**Trial sites identification**
In CRM, we have the database to capture the recruitment data on the clinical trials handled by our study coordinators at each trial site across Malaysia which started from the year 2012. The database includes important information regarding the patient recruitment number for each key therapeutic area. Every month, CRM SCs will update the database and the recruitment specialist will then analyse the data according to different parameters. The following criteria were included for the analysis:

- Recruitment started on the 1st January 2012 onwards (this cut-off was chosen as the database was established in 2012); and
- Recruitment closed on or before 31st December from 2018 to 2019

Note: Trials which were terminated earlier or withdrawn are not included in the analysis.

**Data extraction**
Data was extracted from four major fields in the database which includes 1) trial details (e.g. title, site, region and therapeutic area); 2) study timelines (e.g. site initiation visit (SIV) date and site activation date); 3) recruitment summary (e.g. recruitment target, number of patients randomised); and 4) description of barriers and the strategy used related to each trial. The data was further categorised into regional sectors across Malaysia i.e. northern (Perak, Kedah, Perlis and Pula Pinang), central (Kuala Lumpur and Selangor), southern (Putrajaya, Negeri Sembilan, Melaka and Johor), east coast (Pahang, Terengganu Kelantan and east Malaysia (Sabah and Sarawak).

**Data analysis**
The data was analysed using Microsoft Excel version 10. Descriptive statistics (frequencies and percentages) were used to present information and patterns of trials in 2018 and 2019. The $\chi 2$ test was used to compare the number of trials in 2018 and 2019 with respect to the different characteristics of the trials used.

## Results

**Characteristics of the trial sites**
From our database, a total of 241 trial sites fulfilled the inclusion

criteria and were included in the analysis. Table 1 summarises the characteristics of the trial sites that completed recruitment in 2018 and 2019. Most of the trial sites were involved in oncology trials (26.6%), followed by nephrology trials (10.4%) and paediatric trials (8.7%). Moreover, most of the trial sites were from central Malaysia (25.7%), with 57.7% of the trial sites having a target recruitment of five subjects and below, while the majority of the recruitment period falls under one year (51.9%).

**Comparison of trial sites from the year 2018 and 2019**

There were significant differences in the recruitment target and recruitment achievement as shown below for year 2018 in comparison to 2019 (Table 1). In 2019, most of the recruitment targets are made up of more than five subjects and most of the trial sites have achieved the recruitment target of 100% and more (p-value <0.05). In 2018, the percentage of sites that achieved their recruitment target is 41%, and it increased to 62% in 2019 (Figure 1).

**Discussion**

Failure to enrol and retain an appropriate number of participants into clinical trial results in the reduction of statistical power to prove the hypothesis, prolongs study duration time, drains scarce research resources and threatens the validity of research results[6]. There are many barriers to patient recruitment in clinical trials as reported in other literature, including the complexity of study protocol, lack of awareness about clinical trials in patients, and sociocultural issues related to trial participation[7]. Despite the barriers reported from our analysis, we have found that the recruitment rate was improved from 2018 to 2019. It is believed that the following active initiatives taken by CRM have supported the recruitment performance at the trial sites:

**1. Active Monitoring and Constant Communication with Relevant Stakeholders**

CRM, through the support of study coordinators placed at the hospital and the recruitment specialist who centrally monitors the recruitment data, which has shown improvement to recruitment performance at the trial sites. Active communication to discuss possible new recruitment strategies with the relevant stakeholders (i.e. investigators and sponsors/contract research organisation) kicks in whenever there are recruitment challenges seen at the trial sites. CRM believes this is a shared responsibility for recruitment and our strategy is in line with a study conducted by Rashmi Ashish Kadam[7], where he suggested that it is best to build a relationship with the players involved in the specific trials and always keep a regular contact with the site staff. Lou Shapiro[8] also reported that in order to ensure success in recruitment, communication with medical doctors and support site staff is important.

**2. Create Awareness of Clinical Trials Among the Public**

CRM fully supports educating the public on clinical trials and creates awareness of such topics to the nation. A series of clinical trial promotions such as 'I am Aware' and a 'Clinical Trial Day' were conducted to support this. The activities were done in either hospitals

| Characteristic | Total N=241 | 2018 Total (n): 117 n (%) | 2019 Total (n): 124 n (%) | *p*-value |
|---|---|---|---|---|
| Therapeutic area | | | | - |
| Oncology | 64 (26.6%) | 32 (27.4%) | 32 (25.8%) | |
| Cardiovascular | 20 (8.3%) | 11 (9.4%) | 9 (7.3%) | |
| Endocrinology | 3 (1.2%) | 3 (2.6%) | - | |
| Rheumatology | 10 (4.1%) | 7 (6.0%) | 3 (2.4%) | |
| Nephrology | 25 (10.4%) | 16 (13.7%) | 9 (7.3%) | |
| Haematology | 7 (2.9%) | 4 (3.4%) | 3 (2.4%) | |
| Gastroenterology | 16 (6.6%) | 10 (8.5%) | 6 (4.8%) | |
| Infectious Disease | 4 (1.7%) | 3 (2.6%) | 1 (0.8%) | |
| Paediatric | 21 (8.7%) | 6 (5.1%) | 15 (12.1%) | |
| Neurology | 12 (5.0%) | 4 (3.4%) | 8 (6.5%) | |
| Psychiatry | 3 (1.2%) | 3 (2.6%) | - | |
| Respiratory | 7 (2.9%) | 7 (6.0%) | - | |
| Others | 50 (20.7%) | 11 (9.4%) | 39 (31.4%) | |
| Region | | | | 0.34 |
| Northern | 62 (25.7%) | 32 (27.4%) | 30 (24.2%) | |
| Central | 73 (30.3%) | 36 (30.8%) | 37 (29.8%) | |
| East Malaysia | 43 (17.8%) | 15 (12.8%) | 28 (22.6%) | |
| East Coast | 24 (10.0%) | 14 (12.0%) | 10 (8.1%) | |
| Southern | 39 (16.2%) | 20 (17.1%) | 19 (15.3%) | |
| Recruitment target | | | | <0.005* |
| ≤5 | 139 (57.7%) | 80 (68.4%) | 59 (47.6%) | |
| >5 | 102 (42.3%) | 37 (31.6%) | 65 (52.4%) | |
| Recruitment period | | | | 0.06 |
| ≤ 1 Year | 125 (51.9%) | 68 (58.1%) | 57 (46.0%) | |
| >1 Year | 116 (48.1%) | 49 (41.9%) | 67 (54.0%) | |
| Recruitment achievement | | | | <0.005* |
| Not achieved | 116 (48.1%) | 69 (59%) | 47 (37.9%) | |
| Achieved 100% | 62 (25.7%) | 29 (24.8%) | 33 (26.6%) | |
| Overachieved >100% | 63 (26.1%) | 19 (16.2%) | 44 (35.5%) | |

*Significantly difference with *p-value* < 0.05

*Table 1: Characteristics of trial sites*

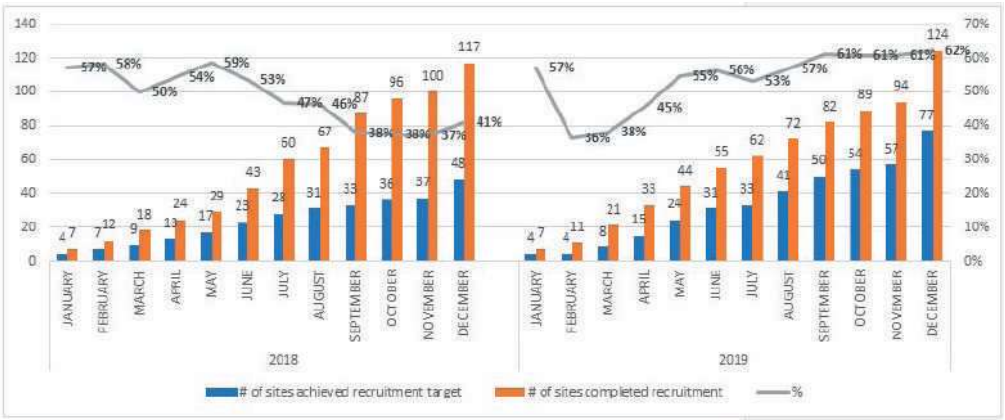


*Figure 1: Comparison of recruitment achievement in the year 2018 and 2019 (cumulative data from previous month)*

or public or private institutions where clinical trial information was shared with the public through our knowledgeable staff. Volunteers who had an interest in participating in clinical trials (healthy volunteers or patients) may also fill up the consent form for trial mapping through our internal database later, i.e. the information of the volunteers will be forwarded to respective trial sites with active recruitment for possible participation if eligible. In 2019, we conducted eight campaigns at different hospitals, with more than 600 volunteers registered, and we have seen positive outcomes where patients were successfully randomised into trials.

In addition to this, CRM has also put up an online platform on our website for the public to register if anyone is interested in participating in a clinical trial. This is called 'Find a Clinical Trial' (FACT) and the following are included on the website:

a) The disease of interest in active recruitment stage
b) The location of the trials being conducted

The participants can register themselves through FACT and the relevant information will be shared to the participating sites to further determine their eligibility for participation. In 2019, we have received more than 20 volunteer registrations and we have seen the positive outcome of patient enrolment in the study. With the positive progression observed, CRM has also started to reach out to relevant patient support groups to advertise the FACT website, hoping to attract a more targeted patient population in patient recruitment.

### 3. Training

CRM conducts training in 'Recruitment and Retention' for investigators and health professionals who have an interest in hospitals. The training was done through lectures and interactive case scenarios among the participants to discuss the recruitment challenges and new recruitment strategies. In 2019, we conducted seven training sessions at the trial sites across Malaysia with more than 200 participants.

### Conclusion

The recruitment performance for the studies handled by CRM SCs have improved from 2018 to 2019. Several key initiatives taken by CRM started in 2018 including active engagement with relevant stakeholders, close monitoring and creating awareness of clinical trials among the public, where training has brought positive progression to the recruitment status in Malaysia.

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Joanne Yeoh graduated from University of Melbourne, Australia with a Bachelor of Biomedical Science. She has vast experience in clinical research operation which she has done for 15 years and was supporting the Clinical operations across Malaysia, Singapore, Taiwan and Hong Kong in the CROs prior joining CRM. Joanne is currently the Head of Clinical Operations in CRM.

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