Investigator-Initiated Clinical Trials in Malaysia and the Role of the Clinical Research Centre of the Ministry of Health

A Fa S Sivanandam*, Y K Hon*, S Yuen, P Muninathan*, P P Goh*, T O Lim***

*Clinical Research Centre, Level 3 Dermatology Block, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Malaysia, **Klinsel Sdn. Bhd., Suite 16.03, 16th Floor, IGB Plaza (known as Plaza Permata), No. 6, Jalan Kampar off Jalan Tun Razak, 50400 Kuala Lumpur, Malaysia

SUMMARY

The objective of this review is to better understand the concept of investigator-initiated trials and its benefits. While investigator-initiated trials can be an invaluable tool, there are several challenges in its initiation and management. However, it is for these reasons that Clinical Research Centre (CRC) had developed the Investigator Initiated Trial (IIT) Programme where financial support and technical assistance are provided to local investigators embarking on their own clinical trials. In the course of preparing the review, we found that the inclination of investigator-initiated trials has yet to be well established in Ministry of Health, Malaysia. Given the potential and impact of such trials, clinicians should be aware of their ability as well as the availability of a supportive network in mobilising their concerted research efforts. Greater research collaboration among investigators could foster more innovative, insightful and constructive research.

INTRODUCTION

An investigator-initiated research is defined by the US Department of Health and Human Services as "research funded as a result of an investigator, on his or her own, submitting a research application."

The Code of Federal Regulations (CFR) describes a sponsor-investigator as "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed." An investigator is the individual "who actually initiates and conducts a clinical investigation" and, for research conducted by a team, is "the responsible leader of the team." The CFR further states that "the sponsor-investigator is required to submit all technical information supporting the Investigational New Drug (IND)," even if the new drug is not used for the purpose of marketing not under manufacturer's IND"[1].

As defined by World Health Organisation (WHO), a clinical trial is 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.' Investigator-initiated trials (IITs) may include treatment trials, prevention trials, diagnostic trials, screening trials and quality-of-life trials. Each type of trial is with an aim to investigate a particular aspect of the efficacy on an intervention.

The primary objective of an investigator-initiated research is academic and healthcare management rather than commercial purposes. The medical significance of IITs stems from them ensuring research independent from economic interests. Furthermore they often generate new therapeutic concepts, which might not be of interest to pharmaceutical companies but which are fully derived from academic research and initiative. As sponsor-investigator both initiates and conducts the investigation of own interest, he/she is more adamant in the achievement of the trial objectives.

In view of its primary objective, benefits of IITs are apparent from several perspectives:

- An invaluable tool in exploring questions such as comparative efficacy of one drug over another or a medical management with surgical interventional management, strategies to ease drug dosage schedules, quality of life issues, alternative systems of medicines. These are the objectives of concern in IITs and are not frequently explored in sponsored trials. New drug development or expanding the indication profile of drugs is the main priority for pharmaceutical company-sponsored trials. Now findings of these trials definitely have important bearing for practice and for establishing health related policies[3]. This is definitely in line with the primary goal of IIT which is to make scientific contributions and these new discoveries will ultimately lead to the advancement in medical diagnosis, treatment and prevention.
- A valuable component in evidence-based clinical practice.
- Since an IIT is not fully sponsored by the industry, thus it is more impartial. In fact, a report documenting combined data from more than 1100 studies showed that industry-sponsored clinical trials are "significantly more likely to reach conclusions that were favorable to the sponsor than were non-industry studies", possibly because of publication bias or selection of an inappropriate comparator to the drug being evaluated[4].

However, it takes a lot to initiate and manage a clinical trial, more so an IIT where a much higher level of administrative effort is often required of investigators. Key challenges are:

1. Lack of internal support, i.e. requiring the cooperation of a multidisciplinary team of specialists such as project managers, biostatisticians, data managers, pharmacists and monitors. This in turn raises expenses considerably.
2. Inexperience in the concepts of clinical trials and its implications such as ethical and legal considerations, trial design and protocol development, study initiation and monitoring, safety surveillance, as well as data management.
3. Financial constraints as the conduct of a trial incur cost such as study equipments, laboratory testing, logistics, human resources and other miscellaneous costs.

The fundamental difference between an investigator-initiated clinical trial and a sponsored clinical trial is that the industry does not play a leading role in IIT, as there is generally no major benefit- either scientific or commercial. As such the industry is not interested in covering the full cost of the study. In addition, sponsor-investigators have more responsibilities in an IIT as compared to being solely an investigator in an industry-sponsored trial. These responsibilities entail the need for more project resources, i.e. staff, facility and equipment.

The industry may, however, provide some funding for an IIT; although the investigator, department and/or the institution will cover the vast majority of the cost. For those IITs which receive some financial support from the industry, they commonly have a contract in place addressing the funding, responsibilities, indemnity and insurance, publication policy, ownership of data and ownership of any eventual invention of discovery as a result of the trial[2].

Current trends of IIT in Malaysia

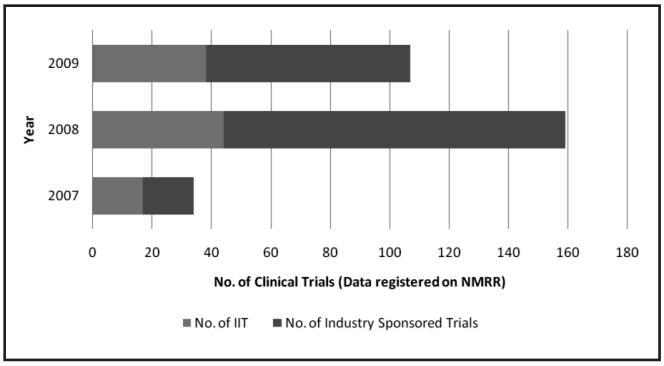

Table I: Number of Clinical Trials Registered on National Medical Research Register from Year 2007 to 2009 (Report extracted on 26 Mar 2010)

Table I illustrates a probable trend of IIT in this country as the data may not be entirely accurate as not all trials are mandatorily required to be registered with the National Medical Research Register (NMRR) and registered trials are mainly from the Ministry of Health institutions hence in such a complete data of trials would not be captured. Hence the limitation of the data but nevertheless it generally shows that the number of IITs has been increasing over the years, i.e. from 17 in 2007 to 38 in 2009. Even so, it is still apparent that the ratio of IITs to Sponsored trials over the years remains relatively low.

As mentioned IITs are mainly academically focused with the objective of translating therapeutic concepts into workable clinical studies and eventually applied to improving clinical practice. Hence it would be interesting to identify current trends of IIT by therapeutic area, i.e. the current interests of fellow healthcare professionals. Such data may not be available but the following table (Table II) does provide an overall depiction of the therapeutic areas in which research has been conducted in recent years.

Table III further illustrates the trend of IIT conducted in this country where the distribution of IITs conducted is tabulated by State. Referring to the data below, it is interesting to note that there is a geographical factor influencing the prevalence of IITs.

Interestingly, Table IV shows that there is considerable number of sites as well as patients involved in IITs considering the less significant total number of IITs conducted.

As mentioned, funding is one of the key challenges in the initiation and management of a clinical trial even more so for IITs where there is most likely a lack of financial support from the more substantial industry grants. Table IV shows the other means of funding for IITs (i.e. non-industry grants) in this country and interestingly self-funding is the most common source.

In summary, an investigator-initiated clinical trial is one in which the principal investigator is required to be well-committed in the conduct of such a clinical trial as the investigator will have to oversee the development, conduct, and management of investigator-initiated trials: tasks of which include protocol development, the peer review process, study conduct, data capture procedures, financial and clinical resources, and publication[1].

Investigator –initiated trials (IITs) in Clinical Research Centre (CRC) Network – Past, Present & Future

Establishment of CRC Network

The CRC Network was established in year 2000 to promote the conduct of clinical trials supported by the Ministry of Health (MOH), Malaysia. Clinical Research Centre, Hospital Kuala Lumpur was the first to be established and the network has grown to a current seventeen branches of offices in the various states of Malaysia, each managing its own clinical research activities, either within its centre or in collaboration with other centres.

CRC is one of the research organisations under the umbrella of the National Institutes of Health of the MOH. Other research organisations include the Institute of Medical Research (IMR), Institute of Public Health (IPH), Institute of Health Management (IHM), Institute for Health Behavioral Research (IHBR) and Institute for Health Systems Research (IHSR).

The CRC Network is involved in various types of clinical research, namely clinical trials, clinical epidemiology, patient registry and national healthcare statistics initiative.

Table II: Research Registered on National Medical Research Register by Therapeutic Area (Report extracted on 19 April 2010)

	2008			2009		
#	Therapeutic area	No	%	Therapeutic area	No	%
1	Hepatology	20	12.6	Psychiatry	17	20.2
2	Cardiology	17	10.7	Cardiology	12	14.3
3	Oncology	17	10.7	Diabetes Mellitus	12	14.3
4	Diabetes mellitus	14	8.8	Oncology	10	11.9
5	Psychiatry	14	8.8	Infectious Disease	7	8.3
6	Nephrology	11	6.9	Respiratology	7	8.3
7	Haemotology	10	6.3	Rheumatology	6	7.1
8	Infectious disease	8	5.0	Endocrine/Metabolic	5	6.0
9	Gastroenterology	6	3.8	Anaesthesiology	4	4.8
10	Medicine	6	3.8	Haematology	4	4.8

Table III: Distribution of IITs for Research Registered on National Medical Research Register by State (Report extracted on 26 Mar 2010)

#	State	Investigators Initiated Trials			
		Year 2008		Year 2009	
		No. of trials	No. of trials (%)	No. of trials	No. of trials (%)
1	Selangor Darul Ehsan	18	31.03	9	22.64
2	Sarawak	1	1.72	7	15.56
3	Pulau Pinang	8	13.79	4	8.89
4	Johor Darul Takzim	3	5.17	10	22.22
5	Wilayah Persekutuan	10	17.24	7	15.56
6	Perak Darul Ridzuan	1	1.72	1	2.22
7	Sabah	4	6.90	0	0.00
8	Negeri Sembilan Darul Khusus	4	6.90	0	0.00
9	Kelantan Darul Naim	2	3.45	1	2.22
10	Kedah Darul Aman	1	1.72	3	6.67
11	Pahang Darul Makmur	2	3.45	0	0.00
12	Terengganu Darul Iman	2	3.45	0	0.00
13	Melaka	2	3.45	0	0.00
14	Putrajaya	0	0.00	3	6.67
	Total	58	100	45	100

*Note: Total exceeds total number of research registered (c.f. Table I) as a research may be conducted in more than one state

Table IV: Cumulative Number of Investigative Sites and Patient Enrollment for IITs Registered on National Medical Research Register (Report extracted on 26 Mar 2010)

Year	No. of IITs	No. of sites involved	Total no. of patients involved
2008	44	143	3195
2009	38	53	2417

Table V: Distribution of IITs for Research Registered on National Medical Research Register by Funding Source (Report extracted on 26 Mar 2010)

#	Funding Source	Number of IITs	
		Year 2008	Year 2009
1	International Grant	2	1
2	MOH Grant	8	2
3	University Research Grant	-	1
4	Self-Funding	32	32
5	Others	2	4
	Total	44	40

*Note: Total does not correlate with total no. of IITs (c.f. Table I) as an IIT may have different sources of funding

Clinical trials conducted in CRC Network

The CRC Network conducts both IITs and industry sponsored-trials. In addition, the network also provides clinical trial-related services such as professional development courses to train investigators and other healthcare professionals in the conduct of clinical research, as well as organising regular research consultative clinics as a service for clinicians working in the MOH to assist them in overcoming any problems which may arise during the course of their clinical research efforts.

Under the purview of National Institutes of Health (NIH), the CRC Network promotes the conduct of quality and ethical clinical research to improve patient outcome.

Significance of IIT in Malaysia

It has been shown that findings of several IITs have not just made an impact academically but also played significant role in shaping current medical practical guidelines in Ministry of Health.

A randomised, multicentre, open-label trial evaluating two peritoneal dialysis systems or also known as the CAPD Trial[5] had a decisive impact on the Ministry of Health policy on utilisation of the type of peritoneal dialysis system in its dialysis program.

Another example would be a controlled randomised trial evaluating the efficacy of mycophenolate mofetil in the induction therapy of proliferative lupus nephritis – the second of such trial in the world to confirm the efficacy of this new immunosuppressant agent[6].

Apart from establishing efficacious data, another IIT with the aim of establishing therapeutic equivalence of a biogeneric and original product was conducted[7,12]. The study is one with economical implications as original epoetin is costly hence with proven efficacy of a biogeneric epoetin, treatment cost would be reduced thereby improving access to therapy. Being the first ever comparative study of a biogeneric and original product, the necessity for rigorous evaluation on biologics was also established.

From the examples above, it is apparent that the conduct of IITs improves the knowledge base for both clinicians and investigators and may shape current medical practice to suit the desired patient outcomes in specific patient demographics within the Malaysian local population. It is also observed that although IITs may be conducted at a small scale, they provide the ground-level evidence which might improve medical practice and often, also the impetus from which further repercussions on medical practice can be actively sought and examined.

As the investigator owns the scientific development of the trial, there is much motivation in conducting the trial to completion and with the ultimate aim of making a scientific contribution by publishing trial results. CRC Network has a good track record of publications as illustrated in the table below.

Year	Number of publications/manuscripts
2002	4
2003	5
2004	7
2005	5
2006	16
2007	18
2008	42
2009	49

Source: Listing of CRC's Research Reports & Journal Publications (31 Dec 2009)

Out of which, the following are some IIT publications conducted by Ministry of Health investigators:

#	Study Title	Publication
1	A Randomized Controlled Trial to Evaluate the Effects of Conversion to Low Calcium Dialysate in Stable CAPD Patients[8]	Nephrology 2008; 13 (Suppl.), A77
2	A Randomized, Multicentre, Open-label Trial to Establish Therapeutic Equivalence Between the Carex and Ultra Disconnect Systems in Patients on Continuous Ambulatory Peritoneal Dialysis[9]	Peritoneal Dialysis International, Vol. 23, Peritoneal Dialysis International, Vol. 23,
3	Direct Stenting Compared to Conventional Stenting in Diabetic Patients Undergoing Elective Angioplasty for Coronary Artery Disease (DECIDE): A multicenter, open label, randomized, controlled efficacy study[10]	American Heart Journal 2004, 148: 1007-11
4	A Randomized, Multicenter, Open-Label Trial to Determine Peritonitis Rate, Product Defect, and Technique Survival Between ANDY-Disc® and UltraBag® in Patients on CAPD (CAPD-II Trial) [5]	American Journal of Kidney Disease 2006; 48 (3): 464-472
5	Randomized trial on the therapeutic equivalence between Eprex and GerEPO in patients on haemodialysis [7]	Nephrology 2007; 12, 431-436
6	Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis6	Nephrology 2007; 12, 431-436
7	A multicenter study to determine the efficacy and safety of a generic atorvastatin [11]	Medical Journal Malaysia, Volume 64, No 2, June 2009 pages 150-154.
8	An Observational Cohort Study to determine the long-term Safety and Efficacy of GerEPO for the treatment of renal anaemia in patients with Chronic Kidney Disease[12]	Nephrology 2009;14:264
9	A Randomized Prospective Study to Investigate the Electrolyte Abnormalities Associated with Oral Sodium Phosphate for Bowel Preparation of Patients for Colonoscopy[13]	Med J Malaysia Vol 64 Supplement B August 2009 pg 76

Role of CRC Network in the Future of IIT Development

The current development of investigator-initiated clinical trials requires much input from all parties of the healthcare arena. Thus, the CRC Network offers an IIT program to provide financial assistance and technical support to local investigators intending to initiate their own clinical trials. Such a program will not only assist in the smooth-running of clinical trials, but also see local investigators through all clinical trial matters, including compliance to trial regulations, trial insurance and professional indemnity, trial design and protocol development, study initiation and monitoring, pharmacovigilance, data management and training services.

The future research areas move towards covering the pertinent healthcare issues at hand, and all research endeavours should ideally receive adequate supporting resources including funding, a team of well-motivated research personnel and properly laid-down research guidelines and protocols. The current spectrum of clinical trial services rendered by clinical trials unit (CTU) in CRC HKL is one example in which the CRC Network is providing a supporting network of resources to facilitate the initiation, conduct and completion of clinical trials.

Besides, greater research collaboration between industry and academy should foster a better research effort among them. The future direction of the CRC Network is to conduct a better conglomeration of high-quality clinical trials that not only increases scientific value of clinical research, but also spurs other researchers to move towards more innovative, insightful and constructive research.

CONCLUSION

The aims of this description are to provide a fair and balanced view of the current status of IIT in this country as well as the output from the Clinical Research Centre Network (the CRC Network). Though there is limitation to the quantitative figures reported here as data extracted are solely on the basis of trial registration on the NMRR hence information are mainly from the Ministry of Health. By detailing a snapshot of all activities (past and present) conducted within the network, it should enable all potential investigators to understand the supporting role of this network, motivate clinicians to be potential investigators in mobilising their concerted research efforts to uphold the quality of all types of clinical research within all arenas of healthcare in Malaysia.

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