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Conducting Clinical Trials in Singapore

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ABSTRACT

All clinical trials in Singapore will now have to conform to the Medicines (Clinical Trials) Amended Regulations 1998 and the Singapore Good Clinical Practice (GCP) Guidelines 1998. The Medical Clinical Research Committee (MCRC) has been established to oversee the conduct of clinical drug trials in Singapore and together with the legislations in place, these will ensure that clinical trials conducted in Singapore are properly controlled and the well-being of trial subjects are safe guarded. All clinical drug trials require a Clinical Trial Certificate from the MCRC before the trial can proceed. The hospital ethics committee (EC) vets the application for a trial certificate before it is sent to MCRC. The drug company sponsoring the trial has to indemnify the trial investigators and the hospital for negligence arising from the trial. The MCRC, apart from ensuring the safety of trial subjects, has to provide continuing review of the clinical trial and monitors adverse events in the course of the trial. The EC will conduct continuing review of clinical trials. When a non-drug clinical trial is carried out, the EC will ensure that the proposed protocol addresses ethical concerns and meets regulatory requirements for such trials.

There is great potential for pharmaceutical Research & Development (R&D) in Singapore. We must develop our skills and infrastructure in clinical trials to enable Singapore to be a regional hub for R&D of drugs in Asia.

Keywords: clinical trials, drugs, regulations, good clinical practice

INTRODUCTION

Recently, the Clinical Trial Regulations have been amended in conjunction with the launch of the Singapore Good Clinical Practice (GCP) Guidelines by the Ministry of Health and the Asia Pacific Economic Co-operation (APEC) Co-ordinating Centre for GCP in Singapore.

The establishment of the APEC Co-ordinating Centre for GCP in Singapore will provide a platform for APEC countries to come together to address GCP needs and also to provide a common framework for drugs to be evaluated for safety, quality and efficacy.

Hitherto, clinical trials in Singapore have been conducted according to the Medicines (Clinical Trials) Regulations 1978 with reference to the internationally accepted International Conference on Harmonisation (ICH) Guideline for GCP.

The present Singapore GCP Guidelines 1998 is modelled along the ICH Guideline. All clinical trials will now have to conform to the Medicines (Clinical Trials) Amended Regulations 1998 and the Singapore GCP Guidelines 1998.

This paper serves to inform doctors about the new changes involved in the conduct of clinical trials in Singapore.

Historical aspects of the Medical Clinical Research Committee

The Medical Clinical Research Committee (MCRC) was established more than 20 years ago by the Ministry of Health (MOH) to oversee the conduct of clinical drug trials in Singapore. This is a gazetted committee where the members are appointed by the Minister under the Medicines Act 1975, Chapter 176 and the Medicines (Clinical Trial) Regulations, 1978. Before the formation of the National Medical Research Council (NMRC) in 1994, the MCRC also oversees the conduct of all other clinical trials which do not involve 'medicinal products', but unlike Clinical Drug Trials which require Clinical Trial Certificates with its attendant legislated conduct under the Medicines Act, all other clinical trials do not require Clinical Trial Certificates. Before the establishment of the NMRC, the MCRC also administers a yearly sum of $100,000 for medical research grants, usually for grants of $10,000 or less.

The legislations are designed to ensure that clinical trials conducted in Singapore are properly controlled and also to safeguard the well-being of the participants involved.

The MCRC is responsible for the evaluation of the safety and efficacy of all drugs where an application for a Clinical Trial Certificate has been filed by the Principal Investigator (PI).

Clinical trials

Clinical trials can generally be classified into four phases.

Phase I

The first trials of a new drug in humans. The drug is given for a short time to a small number of healthy volunteers or patients suffering from the disease for which the drug is intended.

The aim is to make a preliminary evaluation of the human-pharmacological properties of the drug (pharmacodynamics, pharmacokinetics, tolerance).

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Phase II

Pilot studies. Usually open trials in a small number of patients suffering from the disease for which the drug is intended.

The aim is to make a preliminary estimate as to whether the drug has the intended therapeutic effect, and to determine the appropriate therapeutic dosage range.

Phase III

Wider trials to determine the therapeutic effects of the drug and, as far as possible, the pattern and frequency of adverse reactions. In most cases a comparison with established methods of treatment or other control group procedures will be necessary.

Phase IV

Trials are based on approved indications on drugs awaiting registration in Singapore or have already been registered. Adverse reactions and efficacy are monitored.

Clinical Trial Certificate

The MCRC issues Clinical Trial Certificates for the above phases, usually most of the certificates are for Phases III and IV, pending Registration of the Drug in Singapore. Drugs in Phase IV are usually safe for use and have been shown to have no proven toxic effects and have tolerable minor adverse effects where the benefits of the drug for the disease allows acceptability of the adverse effects.

The drug company sponsoring the clinical trial assists the PI to put up the application for the clinical trial certificate through the hospital's ethics committee to the MCRC. The application details the protocol of the trial and include pre-trial toxicological studies in animals, the patient consent form and the letter of indemnity to indemnify the PI and the Hospital/ Institution.

After the MCRC has approved the trial, the clinical trial certificate is sent to the PI with a copy to the CEO of the Hospital. The trial is then conducted by the PI with the assistance of the sponsor (drug company) usually in the person of a nurse who assists the PI who fills in the case report forms (CRF), arranges for investigations, dispenses the drug, arranges for follow-up visits, checks compliance of drug intake by patients, enquires and goes through questionnaire of adverse effects and track patients who default.

The trial certificate is valid for 2 years. If the trial is not completed at the end of 2 years, a new application is required. A report is submitted by the PI at the end of the trial to the MCRC. Any adverse reaction has to be reported to the MCRC.

What is the present status with regards to monitoring of clinical trials within hospitals?

Before the launch of the Singapore GCP Guidelines, a clinical trial is a tripartite affair between the sponsor (drug company), the PI and the MCRC. The ethics committee of the hospital vets the application for a trial certificate. The monitoring and reports are sent to MCRC.

Any audit is by the sponsor (drug company) as they have an interest to maintain standards to ensure that the trial meets the standards required for FDA (Food and Drug Administration, USA) approval. Therefore it is usually the big trials or multi-centre trials sponsored by the big pharmaceuticals who would set high standards together with the PI, as these are usually the ones requiring FDA approval. Other smaller trials, including those sponsored by the individual departments (academic trials), may not have the optimum requirements for the trial, unlike the big trials where a dedicated Regional Trial Director or Co-ordinator conducts regular site visits to audit and trouble shoot, ensuring compliance with procedures and therefore minimising and preventing misconduct within the trials and seeing to proper archiving of trial records and investigating every adverse effect of the trial.

As far as the hospital is concerned, the trial is left to run on its own, including the small departmental trials. The PI or head of department is ultimately responsible. The hospital leaves the trial very much to the individual PI and the department. It makes no distinction between clinical drug trials requiring certificates from MCRC, non-drug clinical trials and department trials which do not require certificates. There is no hospital procedure for monitoring standards and implementation of trial protocols. Some academic trials in some departments might not have gone through the ethics committee.

As such, the situation at hospital level is quite alarming, though MOH expects the ethics committee of the hospital to play a monitoring role. Presently, all clinical trials are considered experimental and therefore research in nature. The Medical Defence Union (MDU) and Medical Protection Society (MPS) provide cover for negligence arising from research. If there is a lawsuit arising from negligence in a clinical trial, the PI, sponsoring company, hospital and MOH will all be liable. The sponsoring company signing the letter of indemnity to cover the PI and the hospital, will provide cover only in so far as the negligence arises from within the conduct of the trial. There are many potential pitfalls for the unwary or inexperienced investigator, especially one who is doing a clinical trial for the first time.

Changing scene

Singapore, the government has decided will be shaped and poised to become a hub for R&D of drugs. The government, through the Economic Development Board (EDB), will be investing and inviting companies locally as well as overseas, to commit and invest in Singapore as a regional hub in Asia for pharmaceutical R&D. The formation of APEC (Asia Pacific Economic Co-operation) Co-ordinating Centre for GCP in Singapore will spearhead this development.

What this means is that there will be more new drugs developed and brought into Singapore, especially those relevant to the Asian market. There will be a greater need for more clinical trials, not only for Phase IV or III but also II and even Phase I later

on. Through APEC and MOH, a Singapore Good Clinical Practice (GCP) guideline will be implemented in conjunction with the Medicines (Clinical Trials) Amended Regulations, gazetted in April 1998, effective August 1998. All PI will have to conform to these guidelines as clinical trial procedures will have to be strictly observed and hospitals will have to play a larger role in the monitoring of all clinical trials within the respective hospitals.

Principles of Singapore Good Clinical Practice

All clinical trials must be conducted in accordance with the Declaration of Helsinki and the benefits of the trial must justify the risk to the trial subject. Rights, safety and well being of trial subjects must be the main consideration of the investigators. Adequate data must be available to support the proposed trial which must be conducted in compliance with MCRC prescribed protocols.

Consent must be obtained from all trial subjects and the investigators must be qualified. Trial protocols must be scientifically sound and all trial information must be accurately reported, interpreted and verified. Confidentiality of records must be maintained. Systems and procedures that assure quality of the trial must be implemented and all investigational product must comply with GMP standards.

Role of MCRC

The Medicines' Act legislating the conduct of clinical trials has been amended to bring it up to date with current international practice. The MCRC will help to ensure the safety and efficacy of new drugs before they are registered in accordance with the newly launched Singapore Good Clinical Practice Guidelines. The Helsinki Declaration governing the Ethics of Human Experimentation will be observed. Through its monitoring process, it will strive to maintain the highest standards in the conduct of clinical trials. The cardinal principles held by the MCRC is that though clinical drug trials are considered in the realms of research, it is research which embraces the intention to treat a patient (therapeutic) with a particular illness using the newest drug therapy which is believed to be safe and efficacious for the patient. Benefit to the patient must override benefit to science and society, in this pursuit.

It is the responsibility of the MCRC:

1. to ensure the protection of the rights, safety and well being of human subjects involved in a trial,
2. as well as reviewing, approving and providing continuing review of trial protocol,
3. and review of the methods and materials to be used in obtaining and documenting informed consent of the trial subjects.

The terms of reference of the MCRC are:

1. to consider a Pl's application to conduct a clinical trial.
2. to consider the evaluation on toxicological data and to liaise with the Centre for Drug Evaluation if the drug is an investigational drug.
3. to evaluate intermittent and final reports of clinical trials to ensure safety of patient.
4. to evaluate reports of adverse events in the course of clinical trials and to decide whether or not to permit such trials to continue.
5. to audit when indicated.

The following documents shall be submitted to the MCRC:

- trial protocols
- consent forms
- subject recruitment procedures
  written information to subjects
- investigator's brochure
- available safety information
- information about payment and compensation available to subjects.
- investigators' CV

Role of Hospital Ethics Committee

The ethics committees will need to be conversant with the changes to the Medicines Act. They will implement strictly the Singapore Good Clinical Practice (GCP) Guidelines. Apart from the initial vetting to ensure the feasibility, safety, potential efficacy of the drug, scrutinising the trial protocol, checking on the consent form and letter of indemnity for PI and hospital, the EC of hospitals will also monitor all trials under their purview. Just as the PI, the hospitals' EC will be directly accountable to the hospital to ensure that trials are properly conducted in accordance with legislation and GCP guidelines. All manner of clinical trials (drug and non-drug), with and without certification by MCRC should be under the purview of the hospital EC.

Responsibilities of Ethics Committee

1. The EC will safeguard the rights, safety and well-being of all trial subjects and ensure that the clinical research data is credible,
2. The EC will review the CV of the investigator of the proposed trial to gauge his competence,
3. The EC will conduct continuing review of each ongoing trial at regular intervals,
4. When a non-therapeutic trial is carried out, the EC will ensure that the proposed protocol addresses relevant ethical concerns and meets regulatory requirements for such trials,
5. The EC will review the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects.

Terms and reference of the Ethics Committee

1. To review investigator's request to conduct a clinical trial (review medical, scientific and ethical basis of trial).
2. Evaluate safety of on-going trial based on reports from sponsors and investigators.
3. Ensure on-going trials carried out in accordance with Singapore GCP guidelines.
4. Report change of protocol or termination of trial to MCRC.
5. Ensure MCRC has issued Clinical Trial Certificate before allowing the trial to commence.

The following documents shall be submitted to EC:

- trial protocols
- consent forms
- subject recruitment procedures
- written information to be provided to subjects
- investigator's brochure
- available safety information
- information about payment and compensation available to subjects
- investigators' CV

Role of Clinical Trial Resource Centre

Ideally each hospital should have its own Clinical Trial Resource Centre (CTRC) just as the Clinical Trial and Epidemiological Research (CTERU) Unit of the MOH, which functions as the resource centre for MOH.

The CTRC should have a manager or clinical trials co-ordinator who would maintain a database of all clinical trials in the hospital. The CTRC helps the EC to monitor the progress of the trial, adverse effects, status of trial, sends reminders and monitors reports to MCRC. It also helps to co-ordinate site audits, arranges for storage of case report forms and archives all relevant trial material. There should be a statistician to help with the statistical aspect of a trial.

The CTRC could also provide training for company sponsored clinical trial nurses or other personnel involved in clinical trials. It could also help to co-ordinate clinical trials and GCP workshops for PI and their trial nurse and other personnel.

The CTRC could liaise with other CTRCs or the CTERU to co-ordinate multi-centre trials, seminars, or workshops. It could also explore common problems like sourcing for companies to provide insurance to indemnify PI and hospitals. It could also help to process patents for successful PI.

The CTRC can potentially be a business unit worth investing in. It could be a joint venture of the hospital and one or more drug companies. A levy can be imposed on drug companies utilising the facilities of the CTRC. The CTRC can train a pool of clinical trial nurses and sell their services to sponsoring companies. It can also conduct courses and seminars for PI and nurses and generate revenue for its upkeep.

Looking forward

There is great potential for pharmaceutical R&D in Singapore. We must develop our skills in clinical trials to become key players so that we can enable Singapore to function as a regional hub in Asia. We have to train our investigators well so that more pharmaceutical companies will invest in Singapore through EDB. These companies will come to conduct multi-centre trials with Singapore as their headquarters, not only for Phases III & IV but even Phases I & II trials because we are at the gateway of the Asian drug market.

We have to strengthen our infrastructure and build a culture for clinical trials along the Singapore GCP Guidelines in keeping with international practice. We need to develop expertise and facilities for pre-trial animal drug testing and Phases I & II trials and establish systems for trial audits in order to maintain high standards so as to produce credible results. With an international reputation for the conduct of clinical trials, giant pharmaceuticals will invest in Singapore and we will be able to capture the global market.

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