Clinical Trials in Asia Pacific

THE LEGISLATIVE FRAMEWORK GOVERNING CLINICAL TRIALS IN SINGAPORE

This article discusses the key legislative provisions governing clinical trials in Singapore.

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Introduction
Clinical trials fall within the legislative framework of the Medicines Act1 (“the Act”) and are mainly governed by the Medicines (Clinical Trial) Regulations2 (“the Regulations”), promulgated under the Act.

A clinical trial is defined at Section  of the Act as “an investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description by, or under the direction of-

(a) a doctor or dentist to one or more of his patients; or
(b) two or more doctors or dentists, each product being administered by or under the direction of one or other of those doctors or dentists to one or more of his patients, where (in any such case) there is evidence that the medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or products is for the purpose of ascertaining whether, or to what extent the product has, or the products have, those or any other effects, whether beneficial or harmful”.

“Medicinal products” is broadly defined to include any substance or article which prevents or interferes with the normal operation of a physiological function.

The Singapore Guideline for Good Clinical Practice (“SGGCP”), which follows the model of the International Conference on Harmonisation Guideline for Good Clinical Practice, is incorporated into the Regulations by reference, making it a statutory duty for sponsors, principal investigators and certificate holders to comply with the provisions of the SGGCP. A breach of the provisions of the SGGCP may constitute an offence punishable by fine or imprisonment.

1 Cap 176,1985 Rev Ed.
2 2000 Rev Ed.
3 Supra n1, Section 3.
4 Supra n2, Regulations 21 and 22.
Licence

Before any person can conduct a clinical trial, one must apply for and obtain a certificate from the Chief Executive of the Health Sciences Authority (the “Licensing Authority”) under Regulation 5 of the Regulations. A certificate is valid for 2 years from the date of issue. The Licensing Authority may impose such terms and conditions at his discretion. A certificate which has been issued may be suspended or revoked by the Licensing Authority without assigning any reason. However, any person aggrieved by a refusal to issue a certificate or the suspension or revocation of a certificate which has already been issued may appeal to the Minister of Health.

Both the holder of the certificate and the principal investigator must be doctors or dentists. No person apart from a holder of a certificate or any person assisting the holder of the certificate in the clinical trial may treat a subject or administer any test material to him, except in a situation of an emergency, where any doctor may treat a subject (within the context of a clinical trial) if it is in the interest of the subject. There is no express requirement for the person assisting the holder of the certificate to be a registered doctor or dentist. However, to give effect to the intention of the regulation, the person assisting should only act on the direct and express instructions of the holder of the certificate, who remains responsible for the treatment and administration of test material.

The clinical trial may only be conducted at the place specified in the certificate.

Duty to Provide Information to the Licensing Authority

The Licensing Authority has the power to require the holder of the certificate to furnish him with information or report at any time and in any manner.

Specifically, there is a continuing duty on the part of the holder of the certificate to notify the Licensing Authority of the discontinuance of the clinical trial or any changes of the principal investigator during the course of a clinical trial. Serious adverse events which are likely to affect the safety or well being of the subject must also be reported to the Licensing Authority as soon as is practicable. Such serious adverse events are not limited to events which arise in the course of the clinical trial in question but extend to known serious adverse events in similar clinical trials elsewhere.

A “serious adverse event” is defined, for purposes of the regulation, as “any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease whether or not caused by the use of the test material which-

(a) results in death;
(b) is life-threatening;
(c) requires in-patient hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity; or causes any congenital anomaly or birth defect.”

6 Ibid, Regulation 45(4).
7 Ibid, Regulation 2.
8 Ibid, Regulation 15.
9 Ibid, Regulation 8.
10 Ibid, Regulations 9 and 10.
11 Ibid, Regulation 17.
12 Ibid, Regulation 17(2).
The words “unfavourable” and “unintended sign” are used conjunctively, suggesting that if a sign is unfavourable but intended, it would not fall within the definition of “serious adverse event”. Although, in reality, it is difficult to envisage that a clinical trial which intends or foresees an unfavourable outcome for the subject would receive approval to proceed in the first place.

Finally, upon conclusion of a clinical trial, a final report is to be submitted to the licensing authority within 3 months after the completion of the trial, or such longer period as the licensing authority may allow.

Informed Consent

Informed consent of the research subject or, where appropriate, his legal representative is a fundamental requirement of law and ethics. Legislation has prescribed certain requirements which will be discussed below. However, an absence of local case law in this area means that there is no definitive pronouncement on the extent to which information has to be provided to a potential subject (or the person who will give consent on his behalf) or how onerous such a duty might be. Arguably, all information which is relevant to the patient should be disclosed.

This is to be contrasted with the situation of obtaining informed consent for conventional therapy, within the doctor patient relationship, where most lawyers would accept the application of the Bolam Test, which is that whether a doctor has sufficiently disclosed the risks and benefits to the patient would depend on whether the doctor has acted in accordance with a practice accepted as proper by a body of responsible and skilled medical opinion. Inherent in this test is the belief that the doctor is the best person to decide how much in terms of the procedure, risks and benefits should be disclosed, in the best interest of the patient. The application of the Bolam Test to informed consent is not without criticism. However, in the context of clinical trials, the Bolam test should have no application, primarily because in the case of clinical trials, the benefits (if any) and safety of treatment, have not been established and therefore it can be persuasively argued that the subject ought to be told of all known risks, in addition to potential benefits. More so when the trial may have no anticipated or potential therapeutic benefit to the subject.

The extensive requirements set out in the Regulations and SGGCP underpin the importance of obtaining full and informed consent before a subject is recruited for a clinical trial. Some of these provisions are discussed below.

Regulation 11 stipulates who is to give consent in a variety of scenarios. Generally, a person of and above the age of 21, or a married person under the age of 21 is able to give consent for himself. If a person is under the age of 21 and unmarried, consent must be obtained from the person and, in addition, the person’s parent, guardian or legal representative. The requirement of the potential subject’s consent may be dispensed with where such person (being unmarried and under the age of 21) (i) lacks sufficient

13 Ibid, Regulation 16(2).
14 Bolam v Friern Hospital Management Committee [1957] 1 WLR 582.
15 Supra n2.
understanding to give consent; and (ii) there is a reasonable prospect that the participation in the clinical trial will directly benefit the person.  

Where a person is unconscious or incapable of exercising rational judgment and it is unlikely that the person will regain consciousness or become capable of exercising rational judgment within the “window period”, consent may be obtained from the person’s spouse, parent, guardian or any person having charge of him and his legal representative, provided that there is a reasonable prospect that the person will benefit from participation in the clinical trial. “Window period” is defined as the period, determined based on scientific evidence, within which the test material must be administered to a subject for it to have the intended potential benefit to the subject.

The consent must be written as well as signed and dated by the person giving consent. Where the person giving consent is unable to sign the written form, the licensing authority may approve an alternative form and manner by which consent may be obtained.

Where a person who is not able to give consent personally and has previously made an advance medical directive under the Advance Medical Directive Act (Cap. 4A), the advance medical directive takes precedence.

In emergency situations, the requirement for consent is dispensed with if the principal investigator and 2 specialists who are not involved in the clinical trial certify in writing that:

(i) the person is facing a life threatening situation which necessitates intervention;
(ii) the person is unable to give consent as a result of his medical condition;
(iii) it is not feasible to request consent from that person or to contact his legal representative within the window period; and
(iv) neither the person, his legal representative nor any family member has informed the principal investigator of his objection to that person being used as a subject in the clinical trial.

The feasibility or otherwise of contacting a person’s legal representative is a subjective determination. It depends in part on the time available within the window period as well as availability of information in tracing the legal representatives or family members. In all cases, best efforts should be made to contact the person’s legal representative.

If a person who is incapable of giving consent for his own participation in a clinical trial subsequently becomes capable of giving consent, the holder of the certificate should at the earliest feasible opportunity give to the subject a full explanation and seek direct consent for the continued participation in the clinical trial.

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16 In cases where a prospective subject is not able to legally give consent (for example, minors or adults with low intelligence) the SGGCP requires that the person (in addition to the person who is to give consent) is informed about the trial to the extent compatible with his understanding and if so capable, the prospective subject should also sign and date the written consent form [SGGCP, 4.8.12]. This gives rise to a situation of potential conflict where the wishes of the prospective subject conflicts with the decision of the person legally identified to give consent on his behalf. Whilst there is no clear answer to such a predicament facing the researcher, the preferred view is probably that if the prospective subject is against participation in the clinical trial, his wishes be respected.

17 Supra n2, Regulation 2.
18 Ibid, Regulation 11(4).
19 Ibid, Regulation 11(8).
20 Ibid, Regulation 12(3).
Clinical Trials in Asia Pacific

In the case of a non-therapeutic trial, care must be taken to obtain consent from the subject personally. In such trials, the consent of the legally acceptable representative may only be sufficient in limited circumstances\(^{21}\).

The conduct of clinical trials in emergency situations are also subject additional requirements prior to approval from the licensing authority. These requirements are set out in regulation 12 of the Regulations.

**Steps Involved In Taking Informed Consent**

In a clinical trial, the process of taking informed consent begins with the drafting of the information sheet containing written information which will be made available to the proposed subject and the written consent form. The information sheet and the informed consent form should have the relevant ethics committee’s written approval\(^{22}\). Once new information becomes available, the ethics committees should be informed, and the information sheets and forms revised and conveyed to subjects from whom informed consent had been previously obtained.

The information conveyed to the person giving consent should be, as far as possible, non-technical and practical. Most importantly, the information must be understood by the recipient\(^{23}\). The person giving consent must also be given ample time and opportunity to ask questions (which should be satisfactorily answered) and to make a decision as to participation\(^{24}\).

The information to be given to the potential subject should include matters prescribed at regulation 14 of the Regulations and Section 4.8.10 of the SGGCP.

The written consent form should be signed and dated by the person giving consent as well as the person who conducted the informed consent discussion. Any new information subsequently given should also be documented\(^{25}\). Informed consent also means that there can be no coercion or undue influence on the potential subject to participate in a clinical trial\(^{26}\). What is less clear is how undue influence may present itself. Any relationship which puts the potential subject in a vulnerable position *vis-à-vis* the person taking consent or involved in a trial increases the likelihood of undue influence, whether intentionally or otherwise. For example, caution must be exercised in employer-employee relationships and where the investigator is also the patient’s treating physician. In such cases, it would be prudent to arrange for the consent to be taken by an independent third party (who must of course be equipped to provide the necessary information and take the consent). Nothing in the consent taking procedure should cause the subject or his legally acceptable representative to waive any legal rights or release the parties involved in the clinical trial from liability for negligence\(^{27}\).

\(^{21}\) SGGCP, 4.8.13; 4.8.14.
\(^{22}\) SGGCP, 4.8.2.
\(^{23}\) SGGCP, 4.8.7.
\(^{24}\) SGGCP, 4.8.8.
\(^{25}\) SGGCP, 4.8.8.
\(^{26}\) Supra n, Regulation 13; SGGCP 4.8.3.
\(^{27}\) SGGCP, 4.8.11.
If the person giving consent is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness must be someone who is able to read and understand the information that is being conveyed. His role is to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by the person giving consent and that consent was freely given. The witness is also required to personally sign and date the written consent form after the requisite information is conveyed\textsuperscript{28}.

A copy of the information sheet and signed written consent form should be given to the subject or his legal representatives before the commencement of his participation in the clinical trial\textsuperscript{29}.

A subject may at any time withdraw from a clinical trial without penalty or losing any of the benefits (eg. medical treatment and follow up) which he would otherwise be entitled to.

**Protocol Compliance and Reporting**

The holder of the certificate is not only answerable to the Ministry of Health, the Licensing Authority, but also to the relevant ethics committees of the hospitals or clinics in which the clinical trial is conducted.

Where the clinical trial is conducted under the auspices of a hospital or a clinic, the provisions of the Private Hospitals and Medical Clinics Act must also be complied with.

Any amendments or changes to the protocol should also be notified to the relevant authorities and ethics committees; and the relevant approval obtained.

**Breach of Provisions**

Non compliance with provisions of the Regulations and, by reference, the SGGCP, may give rise to a fine not exceeding $5,000 or to imprisonment for a term not exceeding 12 months or to both\textsuperscript{30}.

Beyond the scope of the provisions discussed above, researchers must also have in mind other penal sanctions, in other legislative provisions, which can apply to careless, negligent or deliberate research which causes harm and injury.

**Conclusion**

The exposure to legal liability arising from clinical trials may be significantly minimised by careful, detailed and honest disclosure and drafting of the research protocol, licensing approval, ethics committee approval and informed consent from the subject or his legally acceptable representative.\textsuperscript{31}

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\textsuperscript{28} SGGCP, 4.8.9.

\textsuperscript{29} SGGCP, 4.8.11.

\textsuperscript{30} Supra n2, Regulation 22.