

Application of Clinical Trial Certificate of Chinese Medicines in Hong Kong



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(SEPT 2014)

Evidence-based Chinese Medicine Practice



- Through high-quality clinical research
- Transfer the findings from research into practice



Section 129 of the Chinese Medicine Ordinance



- For the purpose of facilitating the conduct of a clinical trial or medicinal test of any proprietary Chinese medicine, the Medicines Board may, upon application, issue a certificate for clinical trial and medicinal test.

Regulation 36B of the Pharmacy and Poisons Regulations



- For the purpose of conducting a clinical trial on human beings or a medicinal test on animals application shall be made in writing to the Committee...
- The Committee may issue a clinical trial certificate or medicinal test certificate...valid for a period not exceeding 2 years....”
- It is therefore a legal requirement to apply for a clinical trial certificate before conducting a clinical trial in HK and this serves to protect the rights, safety and well-being of trial subjects.

Clinical trial



- “Any investigation in human subjects intended to discover or verify the clinical effects, of an investigational product(s), and/or to identify any adverse reactions of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.”

Clinical trial registration



- Any collection of data is indicative of a clinical trial
- Trial registration is required for publication in major journals; unless it is not for publication, all clinical trials should be registered.
- www.ClinicalTrials.gov
- Chinese Clinical Trial Registry (ChiCTR)
(<http://www.chictr.org>)
- www.hkclinicaltrials.com/

The essence of a clinical trial



- **Safety of the study drug**
- **Ethics**
 - Freedom to participate
 - Disclosure of all information related to the study and the study drug
- **Quality of the study**
 - E.g. Cochrane's risks of bias assessment
 - ✦ Random sequence generation
 - ✦ Allocation concealment
 - ✦ Blinding of participants, personnel and outcome assessors
 - ✦ Incomplete outcome data
 - ✦ Selective outcome reporting
 - ✦ Adequate attention to other sources of bias

Documents req. for CT cert. applⁿ



- A completed application form and checklist
- Clinical trial protocol
- Informed consent form
- Letter of approval by the Ethics Committee of the institution
- Investigator's brochure
- The following documents and product of the proprietary Chinese medicine:
 - Its master formula
 - Information on pharmacological and toxicological studies
 - Manufacturing method
 - Drafting note of product specification, product specification, method and certificate of analysis
 - Stability test report(s) The stability tests should be conducted by manufacturers that comply with the requirements of GMP or by laboratories that comply with the requirements of the Chinese Medicines Board.
 - Heavy metals and toxic elements, pesticide residues and microbial limit test reports
 - A sample of the proprietary Chinese medicine
- Documents proving all the manufacturers involved in the production of the proprietary Chinese medicine comply with Hong Kong Good Manufacturing Practice Guidelines for Proprietary Chinese Medicines (GMP) or equivalent (such as a copy of the manufacturer's GMP Certificate)
- A letter from the principal investigator confirming his involvement in the clinical trial concerned
- Curriculum Vitae of the principal investigator and a copy of relevant certificate of registration
- A letter from the Chinese medicine practitioner participating in the clinical trial confirming his involvement in the clinical trial concerned and a copy of his certificate of registration

Investigator/Sponsor/Sponsor-Investigator



- Investigator: a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
- Sponsor: an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
- Most often, the PI of investigator-initiated studies takes up the roles of Sponsor and Investigator.

Clinical trial protocol



- Introduction
- Objective
 - The objective is to examine the efficacy and safety of Gui Pi Tang (GPT), Suan Zao Ren Tang (SZRT), and Tian Wang Bu Xin Dan (TWBXD) as treatment of insomnia.
- Methods
 - Study design
 - ✦ The proposed study is a randomized, placebo-controlled, parallel-group, double-blind trial of GPT, SZRT, and TWBXD for insomnia.
 - Subjects/sample size calculation
 - Treatment protocol
 - ✦ TCM and placebo
 - ✦ Block randomization (e.g. 4 groups the block size should be at least 12, i.e. D, A, D, C, B, A, B, D, B, A, C, C generated by Excel and no way you can predict the next)
 - ✦ Blinding (All treatments are delivered according to the codes)
 - Outcome assessments
 - ✦ Efficacy and safety
 - ✦ Immediate and 4-week posttreatment

Informed consent



- (a) That the trial involves research.
- (b) The purpose of the trial.
- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject's responsibilities.
- (f) Those aspects of the trial that are experimental.
- (g) The reasonably foreseeable risks or inconveniences to the subject.
- (h) The reasonably expected benefits.
- (i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- (j) The compensation and/or treatment available to the subject in the event of trial-related injury.
- (k) The anticipated payment, if any, to the subject for participating in the trial.
- (l) - (t) a total of 20 items



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Investigator's Brochure



- A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects
 - Summary
 - Introduction
 - Physical, Chemical, and Pharmaceutical Properties and Formulation
 - Nonclinical Studies
 - Effects in Humans
 - Summary of Data and Guidance for the Investigator

Systematic review



- English and Chinese language database
 - MEDLINE, EMBASE, China Journals Full-text Database, etc
- Search terms, e.g. (insomnia* or sleep*) and (Gui Pi Tang)
- Year of publication
- Selection criteria
- Data extraction

Nonclinical studies



- E.g. pharmacologic effects, e.g. Effects of GPT on motor activity and duration of pentobarbital sodium-induced sleep
- E.g. acute toxicity

Effects in Human



- Efficacy
- Safety
- [Investigator Brochure in pdf version](#)

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About the study drug



- Its master formula
- Information on pharmacological and toxicological studies
- Manufacturing method
- Drafting note of product specification, product specification, method and certificate of analysis
- Stability test report(s) The stability tests should be conducted by manufacturers that comply with the requirements of GMP or by laboratories that comply with the requirements of the Chinese Medicines Board.
- Heavy metals and toxic elements, pesticide residues and microbial limit test reports
- A sample of the study drug

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What next?



- Wait, feedback, revise, wait,, wait



Conclusion, suggestions and future directions (1)



- To facilitate clinical research in Chinese medicine in HK, the applⁿ of CT cert. has to be more user-friendly
- The time and resources spent on preparing and vetting the documents are huge and it is a no-win situation (to both investigators and regulators)
- To adopt the system used by the Pharmacy and Poisons Board in classifying drug safety and application type.



The safety of trial drugs



- **Three-risk-level Categorization**
 - Type A: No higher than the risk of standard medical care
 - ✦ Trials involving drug registered in Hong Kong if: (a) they relate to the licensed range of indication, dosage and form; or (b) they involve off-label use which is an established practice and supported by sufficient published evidence and/or guidelines.
 - Type B: Somewhat higher than the risk of standard medical care
 - ✦ the drug is used for a new indication (different patient population/disease group); or substantial dosage modifications are made for the licensed indication; or the drug is used in combination in which interactions are suspected.
 - Type C: Markedly higher than the risk of standard medical care.
 - ✦ Trials involving drug not registered in Hong Kong
- **All registered proprietary Chinese medicine place under Type A**

Application schedule of CT cert.



- **Listed schedule (Type A and B)**
 - A completed application form.
 - A completed checklist.
 - A cover letter listing all the submitted documents.
 - A completed clinical trial risk assessment form.
 - Documentary evidence proving that the clinical trial has been approved by the Ethics Committee of the institution where it will be conducted (this may be submitted when available at a later date).
 - The proposed patient information and the patient consent form, in both English and Chinese, or in Chinese only.
 - A copy of the proposed protocol.
 - A sample of the product or substance.
- **Standard schedule (in addition to those listed above) (Type C)**
 - Information of the drug (e.g. investigator's brochure, package insert, other information if applicable, etc.).
 - A sample certificate of the analysis of the drug.
 - Evidence proving that the drug is manufactured in accordance with Good Manufacturing Practices (GMP) (e.g. copy of GMP certificate of the drug manufacturer).

Conclusion, suggestions and future directions (2)



- With the suggested simpler application procedure, we can still maintain patient safety (registered proprietary Chinese medicine used according to the licensed dosage, indication and form) and ethical conduct of a trial (Institutional Review Board to vet).
- The study quality is kept under scrutiny by journal reviewers and editors (only high-quality papers are accepted by good journals) and only good proposals are funded
- Win-win situation to both investigators and regulators

