Guidance Notes for Applicants of the Certificate for Clinical Trial on Medical Device

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1. Introduction

1.1 The Medical Device Administrative Control System and the proposed legislation

The Hong Kong Government pledged to safeguard public health by developing a regulatory framework for medical devices in the Chief Executive's Policy Agenda of 2003. Before legislation was formulated, the Department of Health (DH) introduced in the interim a risk-based regulatory framework termed the Medical Device Administrative Control System (MDACS). It serves to raise public awareness of using safe medical devices, enable traders to familiarise themselves with the future mandatory requirements, and provide an opportunity for DH to obtain feedbacks from the industry to fine tune the long-term regulatory framework.

DH is currently in the process of law drafting. In the proposed legislation, all medical devices are required to be registered with DH except for certain groups of medical devices, which include those to be put under clinical trials. For this latter group, prior issuance of a Certificate for Clinical Trial by the Director of Health will be a prerequisite for lawful conduction of trials using the medical devices concerned. This requirement serves to ensure safe use of the devices on human beings in the course of conduction of clinical studies.

1.2 Purpose of this document

This document provides guidance to applicants who wish to apply, on a voluntary basis under the current MDACS, for a Certificate for Clinical Trial on Medical Device.

2. Clinical Evidence

In order for a medical device to be listed by MDACS, the manufacturer must demonstrate that the device complies with the relevant Essential Principles. To demonstrate such compliance, the manufacturer is usually required to provide appropriate clinical data, which may be either a compilation of the relevant scientific literature and clinical experience of the device concerned, or the results and conclusions of a specifically designed clinical trial. Section 2.1 illustrates the definitions and important concepts of several terms used in this regard.

2.1 Definitions and concepts

Please refer to **Annex I** for details.

2.2 Indications

In making a decision as to whether a clinical trial is required, a manufacturer needs to go through the following steps:

i. To identify the Essential Principles relevant to the device in question.
ii. To identify the clinical data necessary to address residual risks after risk control measures have been taken.
iii. To perform a thorough clinical evaluation to identify existing sources of the clinical data required.

As a general rule, devices based on new or “unproven” technology and those that extend the intended purpose of an existing technology through a new clinical use are more likely to require supporting clinical trial data. Below is a list of examples of circumstances where conduction of clinical trial should be considered:

i. The introduction of a completely new concept of device into clinical practice where components, features and/or methods of action, are previously unknown;
ii. Where an existing device is modified in such a way that it contains a novel feature particularly if such a feature has an important physiological effect; or where the modification might significantly affect the clinical performance and/or safety of the device;
iii. Where a device incorporates materials previously untested in humans, coming into contact with the human body or where existing materials

are applied to a new location in the human body or where the materials are to be used for a significantly longer time than previously, in which case compatibility and biological safety will need to be considered;

iv. Where a device is proposed for a new purpose or function; and

v. Where in vitro and/or animal testing of the device cannot mimic the clinical situation.

2.3 Principles

In order to be justified and to avoid unnecessary experimentation on human subjects, the clinical trial must:

i. be necessary

ii. be designed and conducted properly

iii. be ethical

iv. follow a proper risk management procedure to avoid undue risks

v. comply with all relevant legal and regulatory requirements

3. Application Procedures

Applications for a Certificate for Clinical Trial on Medical Device should be made, by hand or by post, to the following address:-

Medical Device Control Office
Department of Health
Room 3101
31/F Hopewell Centre
183 Queen's Road East
Wanchai
Hong Kong
(Enquiries: 3107 8455)

The application should contain:

a. A completed application form (**Annex II**);

b. A completed Clinical Trial Checklist (**Annex III**);

c. Details of the medical device (**Annex IV**);

d. A copy of the clinical trial protocol (**Annex V**);

e. A letter from the principal investigator confirming his involvement in the

clinical trial;

f. The curriculum vitae of the principal investigator;

g. Documentary evidence that the clinical trial has been approved by the Research Ethics Committee of the institution in which it is to be conducted (this may be submitted if only made available at a later date). The institution concerned should be well recognised to be capable of conducting the trial;

h. Copies of the consent forms of the clinical trial participants; and

i. In case if a Certificate for Clinical Trial on Medical Device was issued previously but has expired/will soon expire, a copy of the previous Certificate(s) for Clinical Trial on Medical Device.

DH will inform the applicant when the Certificate for Clinical Trial on Medical Device is ready. The certificate should be collected in person at the above address and at the following hours:-

Monday to Friday

9:00 a.m. to 1:00 p.m.
2:00 p.m. to 5:30 p.m.

4. Research Ethics Committee Approval

For all clinical trials of medical devices, approval from a relevant Research Ethics Committee has to be sought. This may be obtained prior to or in parallel with the application for the Certificate for Clinical Trial on Medical Device to DH.

5. Grounds for not issuing the Certificate for Clinical Trial

DH will notify the applicant if DH decides not to issue the Certificate for Clinical Trial on Medical Device. In general, unjustifiable risks to public health or safety will lead to non-issuance of the certificate. These may include, but not limited to, the following circumstances:

a. Where there are reasonable grounds to suspect that a device does not satisfy relevant Essential Principles; or

b. Where there are reasonable grounds to suspect that the clinical trial is not

subject to proper controls; or

c. Where there exists expert professional opinion on the proposed clinical trial that the risk benefit analysis given by or on behalf of the manufacturer is inaccurate and that, were the investigation to take place, there would be a significant probability of serious illness, injury or death to the patient or user; or
d. Where there is inadequate/incomplete pre-clinical or animal data in order to make it reasonable for clinical testing to commence; or
e. Where insufficient information has been submitted to enable a proper assessment of the safety aspects of the proposed clinical trial to be made.

The applicant may re-submit revised documentation pertaining to the proposed clinical trial, provided the reason(s) for refusal of the original application has been addressed.

6. Amendments

After the Certificate for Clinical Trial on Medical Device has been issued, all proposed changes to the trial whether relating to the device, aspects of the clinical trial plan, investigators or investigating institutions must be notified to DH.

All requests for amendments should include the following information:

a. The Medical Device Clinical Trial (MDCT) reference number
b. The proposed change(s)
c. The reason(s) for the change
d. A signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party

DH reserves the right to suspend the validity of the Certificate for Clinical Trial on Medical Device if the amendments are considered to increase the risk to either the patient or the user.

7. Labelling of Medical Devices

All medical devices for clinical trial must bear the wording “exclusively for

clinical trial". All clinical investigators should ensure that the wording, i.e. being referred to the device rather than the patient, is clearly understood by all staff using or coming into contact with the device being put under trial and that the device is segregated, where possible, from any similar devices in routine use.

8. Reporting of Serious Adverse Incidents

Holders of the Certificate for Clinical Trial on Medical Device are required to report all serious adverse incidents that occur during a clinical trial within 10 days to DH, whether they are initially considered to be device related or not. This should be reported in a standard form prescribed by DH (**Annex VI**).

A "serious adverse incident" is one which:

a. led to a death
b. led to serious deterioration in the health of the patient, user of others and includes-
   - a life threatening illness or injury;
   - a permanent impairment to a body structure or function;
   - a condition requiring hospitalisation or increased length of existing hospitalisation;
   - a condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place. This includes a malfunction of the device such that it has to be monitored more closely or temporarily or permanently taken out of service
c. led to foetal distress, foetal death or a congenital abnormality or birth defect
d. might have led to any of the above

9. Follow-up Reports

The certificate holder is required to submit to DH a progress report on a yearly basis during the conduction of the clinical trial and a final report at the end of the trial. The standard forms at **Annex VII** and **Annex VIII** should be used for this purpose.

The monitoring reports and audit reports will be submitted to DH on request.

10. References

a. Clinical Evidence – Key Definitions and Concepts. Final document. Global Harmonization Task Force. May 2007.
b. Clinical Evaluation. Final document. Global Harmonization Task Force. May 2007.
c. Clinical Investigations. Working Draft Document. Global Harmonization Task Force. 29 January 2008.
d. Guidance for Manufacturers on Clinical Investigations to be carried out in the UK. EC Medical Devices Directives. Medicine and Healthcare products Regulatory Agency. June 2008.
e. Information for Clinical Investigators. EC Medical Devices Directives. Medicine and Healthcare products Regulatory Agency. July 2009.
f. Access to Unapproved Therapeutic Goods – Clinical Trials in Australia. Therapeutic Goods Administration. Department of Health and Ageing. Australian Government. October 2004.

Medical Device Control Office
Department of Health
Hong Kong Special Administrative Region
November 2009

Annex I

Definitions and concepts

Clinical investigation

This is the systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device. This term is synonymous with “clinical trial” and “clinical study”. It includes feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing approval. In general, it does not include routine post- market surveillance, e.g. investigation of complaints, individual vigilance reports, and literature review.

Clinical data

This is the safety and/or performance information that are generated from the clinical use of a medical device. Sources of clinical data may include:

1. Results of pre- and post-market clinical investigation(s) of the device concerned;
2. Results of pre- and post-market clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device; and
3. Published and/or unpublished reports on other clinical experience of either the device in question or a justifiably comparable device.

Clinical evaluation

This is the assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device when used as intended by the manufacturer. The inputs for clinical evaluation are primarily clinical data in the form of clinical investigation reports, literature reports/reviews and clinical experience. This is a process undertaken by manufacturers of medical devices to help establish compliance with the Essential Principles and should be an ongoing process conducted throughout the life cycle of a medical device. A key goal of clinical evaluation is to establish that any risks associated with the use of the device are acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

Clinical evidence

The clinical data and the clinical evaluation report pertaining to a medical device together constitute the clinical evidence of the device. This is an important component of the technical documentation of a medical device which allows the manufacturer to demonstrate conformity with the Essential Principles. Clinical evidence should be reviewed and updated throughout the product life cycle by the manufacturer as new information relating to clinical safety and performance is obtained from clinical experience during marketing of the device in question and/or comparable devices.

Annex II

The Medical Device Administrative Control System

Application for Certificate for Clinical Trial on Medical Device

1. Applicant's Particulars		
Name		
Address		
Telephone no.		
Fax no.		
Email address		
2. Details of the Medical Device		
Generic name		
Make		
Model		
Classification		
3. Clinical Trial Details		
Title of the trial		
Previous Certificate for Clinical Trial on Medical Device issued? (please tick)	☐ Yes. Previous MDCT ref. no._____ ☐ No	
Principal investigator	Name	
	Address	
	Telephone no.	
	Fax no.	
	Curriculum vitae	
Other investigators	Name	
	Address	
	Telephone no.	
	Fax no.	

Single or multi-centered? (please tick)	☐ Single-centred ☐ Multi-centred		
Institution conducting the trial	Name		
	Address		
Study site(s) in HK	1	Name	
		Address	
	2	Name	
		Address	
	3	Name	
		Address	
Study site(s) outside HK	1	Name	
		Address	
	2	Name	
		Address	
	3	Name	
		Address	
Type of sponsorship (please tick)	☐ Investigator initiated ☐ Medical device company initiated Name of company:_____ Address:_____		
Recruitment size			
Study period			

I hereby declare that the information given in this application is true and correct. I agree to submit serious adverse incidents reported related to the medical device under trial, yearly progress reports and the final study report if the application is approved and the trial proceeds.

Name: _____ Signature: _____

Post: _____ Date _____

Annex III

Clinical Trial Checklist

Documents		**Yes**	**No**
1	The completed application form		
2	This checklist		
3	Details of the medical device		
4	A copy of the clinical trial protocol		
5	A letter from the principal investigator confirming his involvement in the clinical trial		
6	The curriculum vitae of the principal investigator		
7	Letter of approval by the Research Ethics Committee of the institution in which the trial is to be conducted (this may be submitted if only made available at a later date)		
8	Copies of the consent forms of the clinical trial participants		
9	A copy of the previous Certificate(s) for Clinical Trial on Medical Device (in case if a Certificate for Clinical Trial on Medical Device was issued previously but has expired/will soon expire)		
Others			
10	Photograph/diagram/sample of the device if appropriate		
11	A copy/photograph of the label (including the wordings of “exclusively for clinical trial”) on the medical device		

Annex IV

Details of the Medical Device

Information on the medical device in question should at least include the followings:

General information

- Generic name of device
- Make
- Model
- Classification
- Manufacturing country

Specific information

- Brief description of device and other devices designed to be used in combination with it.
- Identification of any features of design that are different from a previously similar marketed product (if applicable).
- Details of any new or previously untested features of the device.
- Summary of experience with any similar devices manufactured by the company including length of time on the market and a review of performance related complaints.
- Risk benefit analysis to include identification of hazards and estimated risks associated with the manufacture (including factors relating to device design, choice of materials, software) and the use of the device (ISO 14971), together with a description of what actions have been taken to minimize or eliminate the identified risk.
- Description of any materials coming into contact with the body and if so, description of such materials, why such materials have been chosen, and which Standards apply (if relevant).
- Identification of any pharmacological components of device with description of intended purpose and previous experience with the use of this substance.
- Identification of any tissues of animal origin incorporated within the device together with information on the sourcing and collection of the animal tissue(s) prior to manufacturing operation; and details with regard to validation of manufacturing procedures employed for the reduction or inactivation of unconventional agents.
- Identification of any special manufacturing conditions required and if so how

such requirements have been met.

- Identification of packaging used for sterilisation of device.
- A summary of the relevant standards applied in full or in part, and where standards have not been applied, descriptions of the solutions adopted to satisfy the requirements of the Essential Principles.
- Instructions for use.
- Identification of any provisions been made by the manufacturer for the recovery of the device (if applicable) and subsequent prevention of unauthorised use.
- Photo/diagram/sample of the device if appropriate.

Annex V

Clinical Trial Protocol

The clinical trial protocol should at least contain the following information:

General information

- Name(s), qualifications, address(es) and the curriculum vitae of the principal investigator and other investigators.
- Name(s) and address(es) of the institution(s) in which the clinical trial will be conducted.
- Description of the intended purpose and mode of action of the device.
- A copy of the approval from the Research Ethics Committee.
- Copies of participants' consent.
- Reference to important relevant scientific literature (if any) with an analysis and bibliography.

Investigation parameters and design

- Title
- Objectives
- Type of clinical trial, e.g. randomized control trial
- Power of the study and sample size
- Inclusion and exclusion criteria
- Randomization and blinding
- Study period
- Endpoints
- Criteria for withdrawal.

Data collection and analysis

- Description of end-points and the data recorded to achieve the end-points
- Describe how participants are followed up, assessed and monitored during the trial
- Description of statistical analysis

In addition, the protocol may cover the following areas where appropriate:

- Access to source data
- Audit plan
- Ethical considerations

- Confidentiality
- Data handling and record keeping
- Financing and insurance
- Publication policy

Annex VI

Serious Adverse Incidents Reporting Form

1. Incident Description		
Information of the victim	Age	
	Sex	
	Past medical history	
Brief description of the incident		
Consequence of the incident (please tick)	☐ Death ☐ Hospitalisation ☐ Serious injury/illness ☐ Mild injury/illness ☐ Nil	
2. Details of the Medical Device		
Make		
Model		
Classification		
Intended use		
Track record		
3. Details of the Manufacturer		
Name		
Address		
Track record		
4. Preliminary Assessment of the incident		

Name: _____ Signature: _____

Post: _____ Date _____

Annex VII

Clinical Trial Yearly Progress Report

Reporting period	dd/mm/yyyy to dd/mm/yyyy
Start date of the clinical trial	dd/mm/yyyy
MDCT reference no.	
Title of the clinical trial	
Targeted no. of participants	
No. of participants recruited	
No. of participants withdrawn	
Reason(s) for withdrawal (if applicable)	

State if there is any change(s) that has been made to the clinical trial during the reporting period and if so details of the change(s) and the date(s) when this was notified to DH.

_____

_____

State if there is any serious adverse incident(s) that occurred during the reporting period and if so details of the serious adverse incident(s) and the date(s) when this was notified to DH.

_____

_____

State if there is any complaint(s) related to the clinical trial that has been received and if so its details.

_____

_____

Describe progress of the trial (i.e. according to plan, lags behind, premature termination)

_____

_____

Name: _____ Signature: _____

Post: _____ Date _____

Annex VIII

Final Report

Reporting period	dd/mm/yyyy to dd/mm/yyyy
Start date of the clinical trial	dd/mm/yyyy
MDCT reference no.	
Title of the clinical trial	
Targeted no. of participants	
No. of participants recruited	
No. of participants withdrawn	
Reason(s) for withdrawal (if applicable)	

State if there is any change(s) that has been made to the clinical trial during the reporting period and if so details of the change(s) and the date(s) when this was notified to DH.

_____

_____

State if there is any serious adverse incident(s) that occurred during the reporting period and if so details of the serious adverse incident(s) and the date(s) when this was notified to DH.

_____

_____

State if there is any complaint(s) related to the clinical trial that has been received and if so its details.

_____

_____

Describe the study duration (i.e. according to plan, extended study period, premature termination)

_____

_____

Briefly summarise study outcomes.

_____

_____

Name: _____ Signature: _____

Post: _____ Date _____