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Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

Background

A revised regulatory framework for the conduct of clinical trials was gazetted on 15 July 2016 and came into effect on 01 November 2016. This article summarises the broad regulatory changes and provides a comparison against the previous regulatory requirements, to aid investigators with applying the changes to their research studies to comply with the Health Sciences Authority's (HSA) requirements for clinical trials.

Updates have been made to the following areas (click on hyperlinks to read more about the respective sections):

1. **Applicable legislation and product controls**
2. **Clinical trial submissions to HSA**
3. **Study responsibilities and post-approval reporting requirements**
4. **Informed consent**
5. **Clinical research materials**
6. **Labelling requirements for therapeutic products and medicinal products**

Investigators are encouraged to refer to the NHG research website for more detailed information on the abovementioned regulatory changes:

https://www.research.nhg.com.sg/wps/wcm/connect/romp/nhgromp/06+conducting+research/regulatory+submission+requirements

(1) Applicable Legislation and Product Controls

Table 1

	Previous Regulatory Controls (Prior to 1st Nov 2016)		Revised Regulatory Controls (Wef 1st Nov 2016)	
Main Act	**Medicines Act 1975**	**Health Products Act 2007**	**Medicines Act 2016**	**Health Products Act 2016**
Clinical Trial Controls	Medicines (Clinical Trials) Regulations Regulates clinical trials involving medicinal products, which include: ▪ Chemical and biologic drugs ▪ Cell, tissue and gene therapy products ▪ Complementary health products, e.g. Chinese proprietary medicines	NA	Medicines (Clinical Trials) Regulations Regulates clinical trials involving medicinal products, which include: ▪ Cell, tissue and gene therapy products ▪ Complementary health products, e.g. Chinese proprietary medicines	Health Products (Clinical Trials) Regulations Regulates clinical trials involving therapeutic products (chemical and biologic drugs). Medical device clinical trials continue to be exempted from regulation, i.e. do not need to be submitted to HSA for review and approval.

From 1st November 2016 onwards, the Singapore Guideline for Good Clinical Practice (SGGCP) will no longer be in use, and will be replaced by the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP). All clinical trials must be conducted in accordance with the revised regulations, ICH GCP and institutional standard operating procedures (SOP).

NHG RESEARCH EDUCATION

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Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

(2) Clinical Trial Submissions to HSA

There will now be 3 types of clinical trial submissions to HSA:

- Clinical Trial Authorisation (CTA)
- Clinical Trial Notification (CTN)
- Clinical Trial Certificate (CTC)

Clinical trials of therapeutic products will require a CTA or CTN, while clinical trials involving medicinal products will require a CTC from HSA. To decide which submission route your study will qualify for, please refer to table 2 below which summarises the characteristics of each application type.

Table 2

	Previous Regulatory Controls (Prior to 1st Nov 2016)	**Revised Regulatory Controls (Wef 1st Nov 2016)**		
Clinical Trial Controls	Clinical Trial Certificate (CTC)	Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)	Clinical Trial Certificate (CTC)
Product type	Medicinal products	Therapeutic products		Medicinal products
Product / study characteristics	Required for all clinical trials involving medicinal products	Required for clinical trials involving: ▪ Locally unregistered therapeutic products. ▪ Locally registered therapeutic products not used in accordance with approved product labelling. ▪ Healthy volunteers (unless approved population is healthy individuals, e.g. vaccines).	Required for clinical involving locally registered therapeutic products used in accordance with product label.	Required for clinical trials involving medicinal products.
Submission timeline to DSRB and HSA	May be submitted concurrently to DSRB and HSA	May be submitted concurrently to DSRB and HSA.	DSRB approval must be obtained before submission to HSA.	May be submitted concurrently to DSRB and HSA.

NHG RESEARCH EDUCATION

Qualité

Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

(3) Study Responsibilities and Post-Approval Reporting Requirements

Tables 3 and 4 below summarise the major changes in study responsibilities and post-approval reporting requirements for clinical trials. For comparison and ease of reference, DSRB's reporting requirements and timelines have also been included into table 4.

Table 3

	Previous Regulatory Controls (Prior to 1st Nov 2016)	Revised Regulatory Controls (Wef 1st Nov 2016)
Sponsor and investigator responsibilities	Regulations reflected only investigator responsibilities but not sponsor responsibilities. [Note: Investigator and sponsor responsibilities were described in the SGGCP.]	Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations require both sponsors and investigators to fulfill their respective legal duties and GCP-related trial functions.

Table 4

Post-approval reporting requirements	Previous Regulatory Controls (Prior to 1st Nov 2016)	Revised Regulatory Controls (Wef 1st Nov 2016)	
	Reporting Requirements to HSA	**Reporting Requirements to HSA**	**Reporting Requirements to DSRB (Included for reference)**
Adverse events	Serious adverse events (SAEs) must be notified, but no time limit was specified in the regulations. *[Note: Reporting timelines for SAEs were stated in the HSA guidance documents.]*	Unexpected serious adverse drug reactions (USADR) must be notified within 7 calendar days.	Local deaths and unanticipated problems (UPIRTSOs) must be notified within 7 calendar days.
Protocol deviations or non-compliances	No legal requirement to notify.	Urgent safety measures and serious breaches must be notified within 7 calendar days.	Protocol deviations or non-compliances must be notified within 14 calendar days.
Changes in clinical trial status	No legal requirement to notify. *[Note: Timelines for notifications related to changes in clinical trial status were stated in the HSA guidance documents.]*	▪ Trial status reports must be submitted every 6-monthly. ▪ Trial suspension or termination must be notified within 15 calendar days. ▪ Trial conclusion must be notified within 30 calendar days.	▪ Study status reports must be submitted annually. ▪ Trial suspension or termination must be notified within 7 calendar days. ▪ Trial conclusion must be notified within 30 calendar days.

NHG RESEARCH EDUCATION

Qualité

Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

(4) Informed Consent

The main changes to the informed consent requirements for clinical trials pertain to vulnerable subjects, namely minors, mentally incapacitated adults and patients in emergency situations. Details of these changes are described in table 5 below.

Table 5

	Previous Regulatory Controls (Prior to 1st Nov 2016)	Revised Regulatory Controls (Wef 1st Nov 2016)
General informed consent requirements	No legal provision on who can take consent from subject. *[Note: Guidelines for consent taking were described in the SGGCP.]*	The informed consent form (ICF) may be explained by a study team member authorised by the principal investigator (PI), but consent must be taken by an investigator who is a medical practitioner.
	For subjects who are unable to read, an impartial witness must be present during the consent process. For subjects who are physically unable to sign the ICF, the form and manner of written consent may be determined by HSA.	An impartial witness should be present during the consent process: ▪ If the person is unable to read (e.g. due to illiteracy, blindness); or ▪ If the person is physically unable to sign the ICF (e.g. stroke patients).
Consent in minors	Consent to be taken from the minor, unless the minor lacks capacity or sufficient understanding to provide such consent. Consent required from parent, guardian or legal representative. Minor must be re-consented for continued participation if he/she becomes capable of giving own consent.	▪ Consent to be taken from the minor, unless the minor lacks capacity or sufficient understanding to provide such consent. ▪ Consent required from legal representative*: ➢ Deputy (appointed under the Mental Capacity Act) ➢ Adult parent ➢ Guardian. ▪ Minor must be re-consented for continued participation if he/she subsequently gains capacity or sufficient understanding during the course of the trial. *[*Note: Appropriate documentation on the relationship of the legal representative to the minor should be kept on file.]*

NHG RESEARCH EDUCATION

Qualité

Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

Table 5 (continued)

	Previous Regulatory Controls (Prior to 1st Nov 2016)	Revised Regulatory Controls (Wef 1st Nov 2016)
Consent for mentally incapacitated adults	▪ Written certification required from principal investigator and independent doctor. ▪ Consent has been obtained from spouse, parent, guardian, any person having charge of the subject, or the legal representative. ▪ Subject must be re-consented for continued participation if he/she becomes capable of giving own consent.	▪ Written certification required from an investigator and independent doctor. ▪ Consent must be obtained from the legal representative*: ➢ Donee (appointed under the Mental Capacity Act) ➢ Deputy (appointed under the Mental Capacity Act) ➢ Any of the following persons in descending order of priority**: spouse, adult child, parent or guardian, adult sibling, any other adult named by the person when he did not lack capacity. ▪ Subject must be re-consented for continued participation if he/she subsequently gains capacity during the trial. *[*Note 1: Appropriate documentation on the relationship of the legal representative to the subject should be kept on file.]* *[**Note 2: The application of the order of priority is subject to several conditions detailed in the applicable regulations.]*
Clinical trials in emergency situations	▪ At the point of CTC submission, written certification required from principal investigator and 2 independent specialists. ▪ Prior to enrolment of each subject, where it is not feasible to obtain consent from subject, his legal representative or any family member, a written certification is required from principal investigator and 2 independent specialists. This certification must be submitted to HSA within 7 working days. ▪ Consent must be obtained from subject, legal representative or family member at earliest feasible opportunity.	▪ At the point of CTA / CTN / CTC submission, written certification required from principal investigator and 2 independent specialists. ▪ Prior to enrolment of each subject, reasonable effort must be made to obtain consent from the subject, his legal representative or any family member. Where such consent is not obtained, a written certification is required from the investigator and one independent specialist. ▪ Consent must be obtained from the subject, legal representative or family member at the earliest feasible opportunity. ▪ Despite having obtained consent from the family member or legal representative, consent should still be obtained from the legal representative or the subject, as the case may be.

NHG RESEARCH EDUCATION

Qualité

Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

(5) Clinical Research Materials (CRM)

CRM include any therapeutic products, medicinal products, medical devices and equivalent placebos manufactured, imported or supplied for the purpose of being used in any clinical research study in accordance with a research protocol. Clinical research studies include both clinical trials regulated by HSA and clinical research studies not regulated by HSA.

CRM are subject to the following regulations:

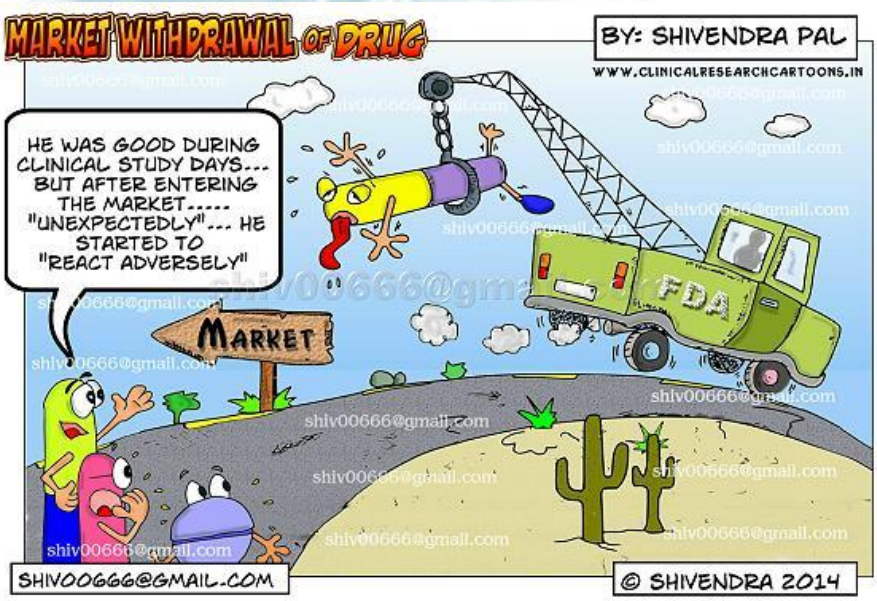
- Medicines (Medicinal Products as Clinical Research Materials) Regulations
- Health Products (Therapeutics Products as Clinical Research Materials) Regulations
- Health Products (Medical Devices) (Amendment) Regulations 2016.

The following regulatory controls apply to CRM:

- **CRM notification to HSA** - Institutions or investigators who are involved in importing or manufacturing of CRM must submit a CRM notification to HSA prior to the initiation of such activities. Investigators who procure CRM from locally marketed sources do not need to submit any CRM notification to HSA.

- **Duties and obligations of CRM dealers** - Manufacturers, importers, suppliers and sponsors of therapeutic products, medicinal products and medical devices are required to fulfill certain duties and obligations related to the CRM. Please refer to the applicable HSA guidances for details.

- **Record keeping for CRM** – The respective retention periods for records of receipt and supply of CRM are specified in the applicable regulations.



NHG RESEARCH EDUCATION

Qualité

Education to facilitate high standards of research conduct

Issue 25, December 2016

UPDATES TO THE REGULATORY FRAMEWORK FOR CLINICAL TRIALS

(6) Labelling of Therapeutic Products and Medicinal Products

While the previous regulations stipulated a fixed set of labeling requirements for all medicinal products, the revised labeling requirements now state the general principles of labeling controls while providing further details on the labeling requirements for different product categories.

Table 6

Previous Regulatory Controls (Prior to 1st Nov 2016)	Revised Regulatory Controls (Wef 1st Nov 2016)
The holder of a certificate shall ensure that all test materials have the following particulars written on the containers: a) The designation, reference number or other identification mark of each item of such material; b) The name and address of the manufacturer; c) The production batch number of the material; d) Name or other identification mark of the subject for whom the test material is intended; e) The date of manufacture and the expiry date of the test material; f) The storage conditions appropriate for each item of test material as may be indicated by the manufacturer; and" g) The words: "This product shall only be used under strict medical surveillance" or "This product shall only be used under strict dental surveillance", as the case may be.	Every investigational* therapeutic product and every auxiliary** therapeutic product used on or after 1 November 2017 in a clinical trial must be labelled with information for all of the following purposes: a) To ensure protection of the subject and traceability; b) To enable identification of the product and the trial; c) To facilitate proper use and storage of the product; d) To ensure the reliability and robustness of data generated in the trial.

The specific labeling requirements for investigational products and auxiliary products are dependent on their registration status in Singapore, as well as the manner in which they are used in the research study. Investigators may consult the applicable regulations and HSA guidances for a detailed breakdown of the specific labeling requirements for each product category.

References

- **Medicines Act 2016 and subsidiary legislation**
- **Health Products Act 2016 and subsidiary legislation**
- **ICH Guideline for Good Clinical Practice E6(R1)**
- **NHG Proper Conduct of Research (PCR) SOPs**
- **HSA Clinical Trial Guidances**

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