CHAPTER 2

REGULATORY REQUIREMENTS

2.1 The Human Biomedical Research Act (HBRA)

The HBRA was passed in parliament in August 2015 and is administered by MOH. The Act was introduced to provide a legal framework and clarity in the rapidly rising fields of HBR and the use of human tissue in research as well as establish clear ethical guidelines for the safety and well-being of research subjects.

The Act sets out two separate but related regulatory frameworks:

a. The Human Biomedical Research Framework; and

b. The Human Tissue Framework

2.1.1 The Human Biomedical Research Framework

This framework governs HBR with the objective of protecting the rights, safety and welfare of human research participants. It also regulates the conduct of certain types of HBR which are considered more "sensitive" such as research involving human eggs or embryos. These are specified in the Third and Fourth Schedules of The Act.

I. HBR Governance

The 3 key entities in the HBR framework are:

1. The Research Institution (RI):

a. Exercises supervision and control over its researchers who conduct HBR, including supervising and proactively monitoring their research to ensure that they comply with the regulatory requirements and controls; and
b. Appoints the IRB to review the research proposals of its researchers, and provides the necessary support to ensure the proper functioning of the IRB.

2. The Institutional Review Board (IRB):

a. Reviews the research proposals of researchers who come under its appointing RI, assessing (among others) the ethics of the study, the qualifications of the researcher(s), and the adequacy of the monitoring system and safety measures put in place to protect the research subjects; and
b. Considering the safety and welfare of the research subjects, makes an independent assessment as to whether to approve (or reject) the proposed research.

3. The researcher who conducts HBR:

a. Must conduct his research under the supervision and control of a RI;

b. Must get his research proposal reviewed and approved by an IRB appointed by his RI;

c. Must ensure that appropriate consent is obtained from each research subject he enrols in his research; and

d. In conducting his research, must not deviate from the approved research proposal unless the deviation has also been reviewed and approved by the IRB.

Researchers should be familiar with the requirements of the approving IRB and his/ her Research Institution (e.g. minimum training requirements).

II. HBR Scope and Definitions

The scope of HBR that will be regulated under the Act includes two main areas:

1. Research that is intended to study –

   a. The prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body; or

   b. The restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; or

   c. The performance or endurance of human individuals,

      And where the research involves –

      i. Subjecting an individual to any intervention (including any wilful act or omission) that has a physical, mental or physiological effect (whether temporary or permanent) on the body of the individual; or

      ii. The use of any individually-identifiable biological material obtained from the human body; or

      iii. The use of any individually-identifiable health information.

2. Research that involves –

   a. Human embryos or human gametes; or

   b. Cytoplasmic hybrid embryos; or

   c. The introduction of any human-animal combination embryo into an animal or a human; or

   d. The introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into an animal at any stage of development (including a pre-natal animal foetus or animal embryo); or

   e. Any entity created as a result of any process referred to in paragraph (c) or (d).

There is also a limited list of research studies that are excluded from the Act and these are set out in the Second Schedule. Examples of exclusions include human psychological / psychiatric tests, IQ tests as well as clinical trials regulated under the Health Products Act and Medicines Act.

III. Requirements for Appropriate Consent and Waivers of Consent

The Act sets out standards for the consent taking process to ensure that potential subjects of HBR studies are satisfactorily informed and understand their roles in the study. Strict requirements have been put in place for research involving vulnerable populations such as those lacking mental capacity or minors as well as with regards to restricted research set out in the Fourth Schedule.

The IRB also plays a key role in guiding the RI and researchers as to when waivers of consent can be granted under the Act.

For more information on informed consent requirements and processes, please refer to chapter 5 Informed Consent and chapter 6 Research in Vulnerable Populations.

IV. Special notifications regarding Restricted Human Biomedical Research (rHBR)

According to HBR 2015, Fourth Schedule, rHBR is defined as:

1. HBR involving human eggs or human embryos.
2. HBR involving:
    a. The following types of human-animal combination embryos:
        i. Cytoplasmic hybrid embryos;
        ii. Human-animal combination embryos created by the incorporation of human stem cells (including induced pluripotent stem cells);
        iii. Human-animal combination embryos created in-vitro by using —
            a. Human gametes and animal gametes; or
            b. One human pronucleus and one animal pronucleus;
            c. The introduction of human stem cells (including induced pluripotent stem cells) into a prenatal animal foetus or animal embryo;
            d. The introduction of human pluripotent stem cells (including induced pluripotent stem cells) into a living postnatal animal but excludes the introduction of such human pluripotent stem cells into immunodeficient mice solely for the analysis of teratoma induction;
            e. The introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into the brain of a living postnatal animal; or
            f. Any entity created as a result of any process referred to in sub-paragraphs (*b*), (*c*) and (*d*).

Prior to starting a <u>Restricted</u> HBR study

Researchers conducting or intending to conduct rHBR must:

i. Ascertain if the research study is a rHBR

ii. Obtain approval from the DSRB and other relevant local regulatory authorities

iii. Obtain approval from the Ministry of Health (MOH)

2.1.2 The Human Tissue Framework (HTF)

This framework protects the safety and welfare of tissue donors through mechanisms such as mandating informed consent from donors, requiring altruistic donations and ensuring that donors' health and welfare are not jeopardised. This framework also seeks to prohibit the commercial trading of human tissue, regardless of whether or not it is used for the purpose of research.

I. HTF Governance

Tissue Bank (TB) means an individual or a body of persons, whether corporate or unincorporate, or other organisation, that carries on or conducts any tissue banking activity but excludes an individual, a body of persons or an organisation that conducts any tissue banking activity solely for the purpose of the person's or organisation's own human biomedical research approved or exempted from review by an institutional review board;

Tissue banking activity means a structured and an organised activity involving human tissue for the purposes of facilitating current or future research or for public health or epidemiological purposes or any combination of such purposes including any of the following activities:

a. The collection, storage, procurement or importation of human tissue;

b. The supply, provision or export of human tissue.

The TB is responsible for the supervision and control over its tissue banking activities, including formulating policies and standards, to ensure compliance with regulatory requirements.

II. Scope and Definitions

Human tissue refers to any human biological material but exclude human biological material specified in the First Schedule of the HBRA. These exclusions include hair shaft, cut without dermal hair root or follicle and naturally excreted bodily fluids such as saliva and sweat.

The key features of this framework include:

1. **Prohibition of Commercial Trading of Human Tissue (With effect from 1 January 2017)**

The Act prohibits the commercial trading of human tissue. It is an offence to buy, sell or advertise the buying or selling of human tissue. However, buying and selling of tissue derivatives and tissue products, which are not considered to be 'human tissue', is permissible. These include substantially manipulated tissue and culture expanded cell lines.

2. Controls on Removal, Storage, Supply and Use of Human Tissue

The tissue donor's consent allows the removal, storage, supply and use of his/her tissue in research. The Act explicitly makes it an offence to compel, coerce, intimidate, deceive or mislead a person into giving his tissue.

3. Confidentiality of Tissue Donors and Regulation of Tissue Banks

The Act requires tissue banks to protect the confidentiality of tissue donors and imposes restrictions on disclosure of individually-identifiable information on tissue donors. Tissue banks will also come under the purview of MOH, which will have powers to inspect and audit them to ensure compliance with the regulatory requirements.

III. Requirements for Appropriate Consent and Waivers of Consent

The Act sets out standards for the consent taking process to ensure that potential donors are satisfactorily informed and understand how human tissues donated would be used. Strict requirements have been put in place for donations involving vulnerable populations such as those lacking mental capacity or minors.

2.1.3 References and Further Reading

For more information on the HBRA and its regulations, please refer to the Ministry of Health website at https://www.moh.gov.sg/policies-and-legislation/human-biomedical-research-act.

2.2 The Regulation of Clinical Trials and Clinical Research Materials

2.2.1 Health Products Act

The Health Products Act regulates the manufacture, import, supply, presentation and advertisement of health products and of active ingredients used in the manufacture of health products and provide for matters connected therewith. This Act is administered by the HSA.

The First Schedule in the Health Products Act specifies the categories of health products to which the regulatory controls in the Act apply. These health products include:

- Medical devices
- Cosmetic products
- Therapeutic products (more commonly known as chemical and biologic drugs)
- Oral Dental Gums
- Cell, Tissue and Gene Therapy Products (CTGTP)

I. Definitions

CLINICAL TRIAL refers to an investigation (of a therapeutic product or Class 2 Cell, Tissue) that involves human subjects, and that is intended to:

a. Discover or verify its clinical, pharmacological or pharmacodynamics effects;

b. Identify any adverse effect that may arise from its use;

c. Study its absorption, distribution, metabolism and excretion; or

d. Ascertain its safety or efficacy.

HEALTH PRODUCT means any substance, preparation or device —

a. That –
   i. Is represented for use by humans;
   ii. Whether because of its presentation or otherwise, is likely to be taken for use by humans; or
   iii. Is included in a class of substances, preparations or devices which are or are ordinarily intended for use by humans, solely or principally for a health-related purpose; and

b. That falls within any of the categories of health products specified in the First Schedule of the HPA;

HEALTH-RELATED PURPOSE means a therapeutic, preventive, palliative, diagnostic or cosmetic purpose, or any other purpose for the promotion or preservation of human health and well-being, and includes the following:

a. Preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or the symptoms thereof, in humans;

b. Compensating for any injury or handicap in humans;

c. Investigating, modifying or replacing any part of the human anatomy or any physiological process in humans;

d. Testing the susceptibility of humans to any disease, disorder or ailment;

e. Influencing, controlling or preventing conception in humans;

f. Testing for pregnancy in humans;

g. Inducing anaesthesia in humans;

h. Destroying or inhibiting micro-organisms that may be harmful to humans; and

i. Cleansing, fragrancing, deodorising, beautifying, preserving, improving, altering or restoring the complexion, skin, hair, nails or teeth of humans.

MEDICAL DEVICE are health products which have a physical or mechanical effect when used on human bodies. These devices are used to:

- Diagnosed, alleviate or treat a medical condition, e.g. X-ray machines, contact lenses, prosthetic knee implants

- Measures or monitor functions of the body, e.g. blood pressure or blood sugar monitoring machines

Products used to maintain or support general well-being without specific medical claims such as body toing equipment, magnetic accessories and massages, are not medical devices.

Medical Device means -

a. Any instrument, apparatus, implement, machine, appliance, implant, reagent for in-vitro use, software, material or other similar or related article that is intended by its manufacturer to be used, whether alone or in combination, for humans for one or more of the specific purposes of —
    i. Diagnosis, prevention, monitoring, treatment or alleviation of disease;

    ii. Diagnosis, monitoring, treatment or alleviation of, or compensation for, an injury;

    iii. Investigation, replacement, modification or support of the anatomy or of a physiological process, mainly for medical purposes;

    iv. Supporting or sustaining life;

    v. Control of conception;

    vi. Disinfection of medical devices; or

    vii. Providing information by means of in-vitro examination of specimens derived from the human body, for medical or diagnostic purposes, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means, and which is not a cell, tissue or gene therapy product; and

b. The following articles:
    i. Any implant for the modification or fixation of any body part;

    ii. Any injectable dermal filler or mucous membrane filler;

    iii. Any instrument, apparatus, implement, machine or appliance intended to be used for the removal or degradation of fat by invasive means.

THERAPEUTIC PRODUCT means any substance that –

a. Is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

   i. For preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or any symptom thereof;

   ii. For investigating, modifying or replacing any physiological process;

   iii. For influencing, controlling or preventing conception;

   iv. For inducing anaesthesia;

b. Has as a constituent any of the following active ingredients:

   i. Any chemical or botanical element, naturally-occurring chemical or botanical material, or chemical product obtained by chemical change or synthesis;

   ii. Any metabolite from a micro-organism;

   iii. Any macromolecule extracted from an organism;

   iv. Any substance derived from a biological system, including any of the following:
      - A whole cell or micro-organism, such as a whole virus or bacterium used as a vaccine;
      - A part of a micro-organism, such as a sub-unit vaccine;
      - A plasma-derived product;
      - A biotechnology-derived substance, such as a protein or polypeptide, or a recombinant vaccine for a preventive purpose;

c. Exerts an inherent effect either pharmacologically, chemically or by other physiological means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and

d. Is not any of the following:
   i. A medical device;

   ii. A cell, tissue or gene therapy product;

   iii. Whole blood or any blood component;

   iv. Any Chinese proprietary medicine;

v. Any homoeopathic medicine;

vi. Any medicated oil or balm;

vii. Any quasi-medicinal product;

viii. Any traditional medicine.

CELL, TISSUE or GENE THERAPY PRODUCT (CTGTP) means any substance that —

a. Is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

   i. For preventing, diagnosing, treating, curing or alleviating any disease, disorder, injury, ailment, handicap or abnormal physical or mental state, or any symptom thereof;

   ii. For replacing, repairing, regenerating or reconstructing any anatomy, or for modifying or replacing any physiological process;

   iii. For regulating, repairing, replacing, adding or deleting a genetic sequence or modifying genetic material;

   iv. For supporting or sustaining life;

b. Has as a constituent any of the following substances or combination of substances:

   i. Viable or non-viable human cells or tissues;

   ii. Viable animal cells or tissues;

   iii. Recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence;

c. Achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and

d. Is not any of the following:

   i. A recombinant vaccine for a preventive purpose;

   ii. An in-vitro diagnostic product;

   iii. Bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use;

iv. Cells and tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure;

v. Organs and tissues that are minimally manipulated and intended for transplant;

vi. Reproductive cells (sperm, eggs) and embryos intended for assisted reproduction;

vii. Whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders.

CLASS 1 CTGT PRODUCT means a CTGT product that —

a. Is the result of only minimal manipulation of human cell or tissue;

b. Is intended for homologous use;

c. Is not combined or used with —
   i. a health product categorised as a therapeutic product in the First Schedule to HPA; or

   ii. a health product categorised as a medical device in the First Schedule to the HPA; and

d. Is assigned by the Authority as a Class 1 CTGT product due to a lower health risk to a user of the product.

CLASS 2 CTGT PRODUCT means a CTGT product other than a Class 1 CTGT product.

II. Clinical Trials of Therapeutic Products and Applicable CTGTPs

Clinical trials of therapeutic products and applicable CTGTPs (i.e. Class 2 CTGTPs) are regulated under the Health Products (Clinical Trials) Regulations. To conduct clinical trials of therapeutic products and applicable CTGTPs in Singapore, a CTA or CTN issued by HSA will be required. Tables 2 and 3 below outline the various criteria and characteristics of CTA and CTN applications.

Table 2: Criteria to determine if a clinical trial requires a CTA or CTN:

Clinical Trial Authorisation (CTA)	Clinical Trial Notification (CTN)
For clinical trials involving: ▪ Locally unregistered therapeutic products or Class 2 CTGTPs. ▪ Locally registered therapeutic products or Class 2 CTGTPs not used in accordance with product registration*.	For clinical trials involving: ▪ Locally registered therapeutic products or Class 2 CTGTPs used in accordance with product registration.

▪ Healthy volunteers (unless approved population is healthy individuals, e.g. vaccines). **Used for a different indication, patient population, dosing regimen, dosage form, etc. from the approved label.*	

Table 3: Key differences between CTA and CTN applications

	Clinical Trial Authorisation (CTA)	**Clinical Trial Notification (CTN)**
Risk level of clinical trial	"Higher risk" trials	"Lower risk" trials
DSRB and HSA submission timelines	Applications to HSA and DSRB may be submitted concurrently	Applications to HSA can only be submitted after obtaining DSRB approval
HSA review timeline	30 working days, or 15 working days for Phase 1 trials solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interactions. 60 working days for Class 2 CTGTP trials.	5 working days

CTA and CTN are valid throughout the duration of the study.

Class 1 CTGTP trials are required to comply with the requirements of the Human Biomedical Research Act (HBRA).

III. Clinical Trials of Medical Devices

Although the sale and supply of medical devices are regulated under the Health Products Act, the conduct of clinical trials of medical devices are not regulated by HSA. Nonetheless, general regulatory controls apply to the use of medical devices in clinical trials [under Health Products (Medical Device) Regulations] and research conduct should comply with Human Biomedical Research Act (HBRA).

2.2.2 Medicines Act

The regulatory controls in the Medicines Act apply to medicinal products such as Chinese proprietary medicines, traditional medicines, homoeopathic medicines and quasi medicinal products (e.g. health supplements).

I. Definitions

CLINICAL TRIAL refers to 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 there is evidence that 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 PRODUCT means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways:

a. Use by being administered to one or more human beings or animals for a medicinal purpose;

b. Use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose.

MEDICINAL PURPOSE means any one or more of the following purposes:

a. Treating or preventing disease;

b. Diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;

c. Contraception;

d. Inducing anaesthesia;

e. Otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

II. Clinical Trials of Medicinal Products

Clinical trials of medicinal products are regulated under the Medicines (Clinical Trials) Regulations. These include clinical trials investigating medicinal products such as Chinese proprietary medicines, traditional medicines, homoeopathic medicines and quasi medicinal products (e.g. health supplements).

To conduct clinical trials of medicinal products in Singapore, a CTC from HSA will be required. Table 4 below outline the criteria and process for CTC applications.

Table 4: Criteria and Process for CTC Applications

Clinical Trial Certificate (CTC) Applications	
Registration status of medicinal product(s)	All clinical trials investigating medicinal product(s) will require a CTC, regardless of the local registration status of the medicinal product(s).
Risk level of clinical trial	All risk levels
DSRB and HSA submission timelines	Applications to HSA and DSRB may be submitted concurrently.
HSA review timeline	30 working days

2.2.4 Observational Clinical Trials

OBSERVATIONAL TRIAL is a research study where:

a. The product is prescribed by a locally registered doctor / dentist to a patient in the usual manner in accordance with the terms of the product registration or product licence;

b. The decision to prescribe the product to the patient is clearly separated from the decision to include the patient in the trial;

c. The assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is not decided in advance by a protocol but falls within the current practice of the locally registered doctor / dentist carrying out the trial.

Observational trials are excluded from the regulatory controls under the Health Products Act and Medicines Act. However, such trials such comply with requirements of Human Biomedical Research Act (HBRA).

2.2.5 Clinical Research Materials (CRM)

Clinical Research Materials (CRM) refer to any registered or unregistered **therapeutic product**, **medicinal product, medical device**, applicable cell, tissue and gene therapy product (**CTGTP**) or **placebo**, that is manufactured, imported or supplied for the purpose of being used in clinical research*, by way of administration to a trial participant in accordance with the research protocol or for a clinical purpose.

**Clinical research refers to any research involving human subjects, and is a collective term comprising clinical trials regulated by HSA as well as clinical research studies not regulated by HSA (e.g. HBRA regulated studies).*

Regardless of whether HSA regulates the research study, the manufacture, import and supply of CRM in Singapore must comply with the respective regulatory controls for CRM as per below (Table 5):

Table 5: Applicable regulations for CRM

Clinical Research Material	Applicable Regulations
▪ Therapeutic products ▪ Class 2 CTGTPs ▪ Class 1 CTGTPs for which the manufacturer / importer / wholesaler notification has not been made to HSA.	Health Products (Clinical Research Materials) Regulations
Medicinal products	Medicines (Medicinal Products as Clinical Research Materials) Regulations
Medical devices	Health Products (Medical Devices) Regulations

I. CRM Notification to HSA

A CRM notification must be submitted to HSA prior to the following:

- Import of any CRM for local clinical research use.

- Supply by the local manufacturer of CRM for local clinical research use, including CRM compounded at the local trial site.

CRM notification is not required for the following:

- Locally registered CRM obtained from local commercial sources
- Import of locally registered CRM for local clinical research use if the importer already has a valid importer's license for the import of CRM
- Supply of a locally registered CRM by its local manufacturer for local clinical research use if the manufacturer has a valid manufacturer's license
- Supply of CRM by a local manufacturer if the manufacture of the CRM being supplied comprises solely of the packaging or labelling of the CRM
- Import of a minimally manipulated CTGTP CRM for local clinical research use by a known importer
- Supply of a minimally manipulated CTGTP CRM by its known manufacturer for local clinical research use

II. Duties and Obligations of CRM Dealers

All parties involved in supplying CRM – including local manufacturers, importers, suppliers and sponsors – must comply with the following duties and obligations relating to CRM.

Table 6: Duties and obligations of parties involved in supplying CRM other than medical device CRM.

Duties and Obligations	Parties			
	Local Manufacturer	Importer	Supplier	Sponsor
All CRM (including locally-registered products)				
Maintain records of receipt and supply	✓*	✓*	✓	✓*
Ensure compliance with labeling requirements	✓*	✓*	✓	✓*
Report unexpected serious adverse drug reactions (USADR) to HSA	-	-	-	✓
Establish and maintain a system of traceability (only for CRM that is a CTGTP)	✓	✓	✓	✓*
Report CRM defects	✓	✓	✓	✓*
Notify HSA 24 hours before recall of CRM	✓	✓	✓	✓*
Additional requirements for locally manufactured or imported CRM				
Ensure the CRM (TP/MP) is of the correct identity and conforms with the applicable standards of strength, quality and purity for the material	✓	✓	-	-
Maintain records of manufacture, assembly and testing	✓	-	-	-
Ensure CRM supply / use only for clinical research purposes	✓*	✓*	✓	✓*
Ensure CRM use only in IRB-approved clinical research	-	-	-	✓
Ensure disposal / export of CRM within 6 months after research completion/ termination	-	-	-	✓
Maintain records of disposal / export of CRM	-	-	-	✓

**Responsibility as "Supplier"; includes local manufacturer, importer, wholesaler, sponsor, investigator where applicable, if the party involved in the activity of supplying a TP/CTGTP as CRM). This is also applicable to TP, CTGTP and MP used in clinical research that is not regulated by HSA.*

Table 7: Duties and obligations of parties involved in supplying medical device for clinical research purposes

Duties and Obligations	Parties			
	Local Manufacturer	Importer	Supplier*	Sponsor
All CRM (including locally-registered products)				
Ensure the CRM (MD) complies with "Safety and Performance Requirements for Medical Devices" in the First Schedule of the Health Products (Medical Devices) Regulations	✓	✓	-	-
Maintain records of manufacture, assembly and testing	✓	-	-	-
Maintain records of receipt and supply	✓*	✓*	✓	✓*
Ensure compliance with labeling requirements	✓	✓	✓	✓*
Report MD defects and adverse effects to HSA	✓	✓	✓	✓*
Maintain records of complaints	✓	✓	✓	✓*
Notify HSA concerning recall	✓	✓	✓	✓*
Notify HSA concerning field safety corrective actions	✓	✓	✓	✓*
Additional requirements for locally manufactured or imported CRM				
Ensure CRM supply / use only for clinical research purposes	✓*	✓*	✓	✓*
Ensure CRM use only in IRB-approved clinical research	-	-	-	✓
Ensure disposal / export of CRM within 6 months of research completion/ termination	-	-	-	✓
Maintain records of disposal / export	-	-	-	✓

**Responsibility as "Supplier"; includes local manufacturer, importer, wholesaler, sponsor, investigator, where applicable, if the party is involved in the activity of supplying a MD for clinical research.*

III. Record Keeping for CRM

The CRM regulations require designated parties to maintain records of manufacture, receipt, supply and disposal of CRM.

Record-keeping for CRM other than medical device CRM must comply with the following requirements.

Table 8: Requirements for record-keeping in relation to CRM other than medical device CRM

This is applicable to any supplier of CRM other than medical device CRM, including; importers; local manufacturers; wholesaler (e.g. distributor), sponsor, investigator or other healthcare professional (e.g. pharmacist) supplying CRM.

	Type of Records		
	Manufacture	**Receipt and Supply**	**Disposal (Including Export or Putting to Other Use)**
Applies to	Locally-manufactured CRM (other than medical device CRM)	All CRM (other than medical device CRM)	Unused CRM (including expired CRM or those which can no longer be used for research) that was imported or locally manufactured is disposed of (e.g. sent for destruction) or exported within 6 months of the conclusion/ termination of the clinical research
Party Responsible	Manufacturer	Any person who supplies CRM, including the importers, local manufacturers, wholesaler (e.g. distributor), sponsor, investigator or other healthcare professionals (e.g. pharmacist).	Sponsor
Required Elements in Records *NB: The records must be kept up-to-date at all times and be available for inspection by HSA upon request.*	All records of the manufacture, assembly and testing of the material, and, records of traceability (for CRM that is a CTGTP).	• Proprietary name (i.e brand name) or other description • Identification number of the CRM (e.g. control number, lot/ batch number) • Details of each receipt or supply, including: - Date on which the CRM was received/ supplied; - Quantity of CRM received/ supplied, and - Name and address of the person from	• Proprietary name (i.e brand name) or other description • Identification number of the CRM (e.g. control number, lot/ batch number) • Details of the disposal, export or putting to some other use, including • The date on which the CRM was disposed, exported or put to some other use,

		whom the CRM was received or to whom the CRM will be supplied.	• The quality of CRM disposed, exported or put to some other use, and • The name and address of the person responsible for the disposal, export of purring to some other use of the CRM.
Duration of Record-Keeping	<u>For registered & unregistered investigational CRM & unregistered auxiliary CRM</u>: • 5 years after completion/ discontinuation of the last clinical trial in which the batch was used <u>For registered auxiliary CRM, the longer of the following periods</u>: • 1 year after the expiry date of the material; or • 5 years after the date of such manufacturer, assembly and testing; and <u>For traceability records relating to CTGTP CRM:</u>	For CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest): • No more pending or planned applications for registration of the TP, CTGTP or MP that was tested in the clinical trial / research • 2 years after the last of such registrations has been granted • 2 years after HSA was informed of the termination of the clinical trial • 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit") - If the clinical trial involves an applicable CTGTP and in the case of a record that relates to the traceability of the product, 30 years after the expiry date of that product or any other shorter period that HSA allows in a particular case; • Any other period as directed by HSA. For CRM supplied for use in a clinical research that is **<u>not</u>** <u>regulated</u> by HSA: • If the CRM is not a CTGTP - 2 years after the supply; • If the CRM is a CTGTP and; - The records do not relate to traceability, 2 years after the supply; or - The records relate to traceability, 30 years after the expiry date of the CTGTP, or any	

	• 30 years after expiry date of the product or any other shorter period that HSA allows in a particular case.	other shorter period that HSA allows in a particular case;

There are additional record-keeping requirements if the clinical research material is a Pharmacy-Only (P) Medicine or a Prescription-only medicine (POM) that is supplied directly to the trial participant, such as in a retail pharmacy setting.

Table 9: Requirements for record-keeping in relation to medical devices (MD) as CRM

	Type of Records		
	Manufacture	**Receipt and/or Supply**	**Disposal (Including Export or Putting to Other Use)**
Applies to	Locally-manufactured MD as CRM	All MD CRM	Imported or locally manufactured MD CRM
Party Responsible	Manufacturer	Any person who supplies MDs as CRM, including the manufacturers, importers, wholesalers, sponsors.	Sponsor
Required Elements in Records *NB: The records must be kept up-to-date at all times and be available for inspection by HSA upon request.*	As required by existing Health Products (Medical Device) Regulations	• Proprietary name (i.e. brand name) or other description of the CRM • Identification number or mark of the CRM (e.g. control number, lot number, batch number, serial number) • Details of each receipt or including: – Date on which the CRM was received or supplied; – Quantity of CRM received or supplied, and - Name and address of person from whom the CRM was received or to	• Proprietary name (i.e. brand name) or other description of the MD CRM • Identification number or mark of the CRM (e.g. control number, lot number, batch number, serial number) • Details of the disposal, export or putting to some other use including: – Date on which the CRM was disposed, export or put to some other use,

		whom the CRM will be supplied.	– Quantity of CRM disposed, export or put to some other use, and - Name and address of person responsible for the disposal, export or putting to some other use of the CRM. The Sponsor must obtain permission from HSA for any unused CRM deems as fit to be put to some other use other than in clinical research before using for that purpose. If permission is granted by HSA for the unused MD CRM to be used for that purpose, the MD will no longer be considered a CRM but is still subject to applicable laws relating to medical devices including the Health Products (Medical Device) Regulations.
Duration of Record-Keeping	• Projected useful life of the MD; or • 2 years after the MD is supplied (Whichever is longer)	For <u>unregistered</u> MD CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest): • No more pending or planned applications for registration of the TP/ MP that was tested in the clinical trial/ research • 2 years after the last of such registrations have been granted	For <u>unregistered</u> MD CRM supplied for use in a <u>regulated clinical trial</u> (whichever is the latest): • No more pending or planned applications for registration of the TP/ MP that was tested in the clinical trial/ research

		• 2 years after HSA was informed of termination of the clinical trial • 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit), or • Any other period as directed by HSA MD CRM (whether registered or unregistered) is supplied for used in clinical research <u>not regulated</u> by HSA, or if the MD CRM is a registered MD, records of receipt and supply must be kept for either: • The projected useful life of the medical device, or • 2 years after the date on which the medical device was supplied, whichever is the longer period	• 2 years after the last of such registrations have been granted • 2 years after HSA was informed of termination of the clinical trial • 6 years after completion of clinical trial (i.e. 6 years after "Last-Patient-Last-Visit), or • Any other period as directed by HSA If the MD CRM (whether registered or unregistered) is supplied for used in clinical research <u>not regulated</u> by HSA, or if the MD CRM is a registered MD, records of disposal must be kept for 2 years after the time when the medical device is put to some other use, dispose of or exported.

2.2.6 References and Further Reading

For more information on the regulatory requirements for clinical trials and clinical research materials, please refer to the following websites:

- Singapore Statutes Online, available at https://sso.agc.gov.sg.
- Health Sciences Authority website, available at https://www.hsa.gov.sg.

2.3 The Personal Data Protection Act (PDPA)

The purpose of the PDPA is to govern the collection, use and disclosure of personal data by organisations in a manner that recognises both the right of individuals to protect their personal data, and the need of organisations to collect, use or disclose personal data for purposes that a reasonable person would consider appropriate in the circumstances.

Scope and Definitions

PERSONAL DATA refers to data, whether true or not, about an individual who can be identified from that data; or from that data and other information to which the organisation has or is likely to have access.

- This includes unique identifiers (e.g. NRIC number, passport number), as well as any set of data (e.g. full name, date of birth, full address etc.) which when taken together would be able to identify the individual.

Researchers should note that the scope of PDPA only applies to identifiable data. The PDPA does not apply to data that is used in anonymised form.

The PDPA takes into account the following concepts:

- Consent – organisations may collect, use or disclose personal data only with the individual's knowledge and consent (with some exceptions);

- Purpose – organisations may collect, use or disclose personal data in an appropriate manner for the circumstances, and only if they have informed the individual of purposes for the collection, use or disclosure; and

- Reasonableness – organisations may collect, use or disclose personal data only for purposes that would be considered appropriate to a reasonable person in the given circumstances.

2.3.1 Data Protection Obligations under PDPA

1. Accountability Obligation

- To undertake measure to ensure that organization meet their obligations under the PDPA such as making information about your data protection policies, practices and complaints process available upon request and designating a data protection officer (DPO) and making the business contact information available to the public.

2. Notification Obligation

- To notify individuals of the purposes for which your organization is intending to collect, use or disclose their personal data.

3. Consent Obligation

- To only collect, use or disclose personal data for purposes which an individual has given his/her consent to.
- To allow the individual to withdraw consent, with reasonable notice, and inform him/her of the likely consequences of withdrawal. Once consent is withdrawn, make sure that you cease to collect, use or disclose the individual’s data.

4. Purpose Limitation Obligation

- To only collect, use or disclose personal data for the purposes that a reasonable person would consider appropriate under the given circumstances and for which the individual has given consent.
- An organization may not, as a condition of providing a product or service, require the individual to consent to the collection, use or disclosure of his or her personal data beyond what is reasonable to provide that product or service.

5. Accuracy Obligation

- To make reasonable effort to ensure that personal data collected by is accurate and complete, if it is likely to be used to make a decision that affects the individual, or to be disclosed to another organisation.

6. Protection Obligation

- To ensure reasonable security arrangements have been made to protect the personal data in your organisation's possesses to prevent unauthorised access, collection, use, disclosure or similar risks.

7. Retention Limitation Obligation

- To cease retention of personal data or dispose of it in a proper manner when it is no longer needed for any business or legal purpose.

8. Transfer Limitation Obligation

- Transfer personal data to another country only according to the requirements prescribed under the regulations, to ensure that the standard of protection is comparable to the protection under the PDPA, unless exempted by the PDPC.

9. Access and Correction Obligation

- Upon request, organisations have to provide individuals with access to their personal data as well as information about how the data was used or disclosed within a year before the request.
- Organisation are also required to correct any error or omission in an individual's personal data as soon as practicable and send the corrected data to other organisations to which the personal data was disclosed (or to selected organization that the individuals has consent to), within a year before the correction is made.

10. Data Breach Notification Obligation

- In the event of a data breach, organisations must take steps to access if it is notifiable. If the data breach likely results in significant harm to individuals, and/or are of significant scale, organisations are required to notify the PDPC and the affected individuals as soon as practicable.

11. Data Portability Obligation

- At the request of the individual, organization are required to transmit the individual's data that is in the organisations' possession or under its control, to another organization in a commonly used machine-readable format.

  Exception may apply to the obligations above. For more information, please refer to Advisory Guidelines on Key Concepts in the Personal Data Protection Act.

2.3.2 Collection, use and disclosure of personal data without consent

Please refer to Second, Third and Fourth Schedule of the PDPA for more information.

2.3.3 References and Further Reading

For more information on the PDPA, please refer to the following websites:

- Singapore Statutes Online, available at https://sso.agc.gov.sg
- Personal Data Protection Commission Singapore, Data Protection Obligations, available at https://www.pdpc.gov.sg