LICENCE CONDITIONS FOR ALL ACUTE HOSPITAL SERVICE, OUTPATIENT DENTAL SERVICE AND OUTPATIENT MEDICAL SERVICE LICENSEES ADMINISTERING OR INTENDING TO ADMINISTER CELL, TISSUE AND GENE THERAPY PRODUCTS MANUFACTURED IN-HOUSE BY HEALTHCARE INSTITUTIONS

IMPOSED UNDER SECTION 13(1) OF THE HEALTHCARE SERVICES ACT 2020

1 Application

1.1 These licence conditions ("**LCs**") apply to all persons that have been licensed under the Healthcare Services Act 2020 ("**HCSA**") to provide:

(1) an acute hospital service ("**AHS**");
(2) an outpatient dental service ("**ODS**"); and/or
(3) an outpatient medical service ("**OMS**"),

that administer or intend to administer, as part of the aforementioned service(s), Cell, Tissue and Gene Therapy Products ("**CTGTPs**") (as defined in paragraph 2.1(1) below) (such persons referred to as "**Licensees**").

1.2 A breach of these LCs may result in regulatory action being taken against Licensees under section 20 of the HCSA, including but not limited to:

(1) suspension or revocation of the Licensee's AHS, ODS, and/or OMS licence(s);

(2) shortening the term of the Licensee's AHS, ODS, and/or OMS license(s);

(3) a direction requiring the Licensee to rectify the contravention, or prevent a recurrence of the contravention; and/or

(4) a direction requiring the Licensee to pay a financial penalty.

1.3 For avoidance of doubt:

(1) the defined terms as used in these LCs shall have the meaning ascribed to them in the HCSA and any Regulations made thereunder, unless otherwise stated;

(2) these LCs do not override a healthcare professionals' duty to make clinical decisions that are in the best interests of each patient; and

(3) the requirements in these LCs are without prejudice, and in addition to the requirements imposed under the HCSA as well as any Regulations and other applicable licensing conditions, directions, codes of practice made thereunder.

2 Definitions

2.1 In these LCs, unless otherwise specified:

(1) "**Cell, Tissue and Gene Therapy Products**" or "**CTGTPs**" means products containing or consisting of:

(a) autologous (obtained from the same individual) or allogeneic (obtained from another individual) human cells or tissue,
(b) animal cells or tissues, or
(c) recombinant nucleic acids (modified Deoxyribonucleic Acids ("**DNA**") or Ribonucleic Acids ("**RNA**") as carriers of a therapeutic gene),

that are, or are intended to be, used for or administered to human beings for the diagnosis, treatment or prevention of human disease or conditions, or to change the appearance or anatomy of an individual. Notwithstanding the above, CTGTPs do not include minimally manipulated cells or tissue that are used in:

(I) tissue and organ transplantation;
(II) the transplantation of haematopoietic stem cells for homologous use;
(III) blood transfusion for treating blood loss or blood disorders; and
(IV) assisted reproduction.

(2) "**Generally Accepted Treatments**" means the following treatments in which In-House Manufactured CTGTPs are accepted for use by a respectable body of medical opinion as conventional treatment for the medical condition —

Treatments using:

(a) autologous chondrocytes, for symptomatic articular cartilage defects of the knee;
(b) *ex vivo* expanded autologous human skin epithelial cells containing stem cells, for severe burns or complex life-threatening wounds; and

(c) *ex vivo* expanded autologous human corneal epithelial cells containing stem cells, for moderate to severe limbal stell cell deficiency after eye burns.

Notwithstanding the above, a treatment is <u>not</u> a Generally Accepted Treatment if:

(I) the quality, safety and efficacy of the CTGTP(s) used in the treatment has/have not been ascertained and verified by the Health Sciences Authority ("**HSA**");
(II) the CTGTP(s) used in the treatment has/have not been registered with HSA; and
(III) the CTGTP(s) used in the treatment is/are used for therapeutic indications other than the Generally Accepted Treatment itself.

(3) "**In-House Manufactured**" means the non-commercial production of CTGTPs by a healthcare institution ("**HCI**"), whether for use by patients of the HCI or to be distributed for use by patients in another HCI. It also includes the HCI "outsourcing" this activity to a third-party commercial entity[1] to manufacture and re-supply the CTGTP back to the HCIs for use by their own patients only.

3 <u>Requirements for use of In-House Manufactured CTGTPs</u>

3.1 The Licensee shall ensure that In-House Manufactured CTGTPs are only used in:

(1) Generally Accepted Treatments;
(2) formal and approved research / clinical trials ("**Research / CT**"); and
(3) innovative salvage therapy[2],

in accordance with all relevant requirements, including those set out in these LCs and applicable legislation.

3.2 The requirements set out in paragraph 3 of these LCs shall apply to the use of In-House Manufactured CTGTPs in Generally Accepted Treatments, Research / CT, and innovative salvage therapy. In addition, the requirements set out in paragraph 4 of these LCs shall apply to the use of In-House Manufactured

[1] To avoid doubt, such third-party commercial entity must still adhere to all relevant requirements, including those imposed under legislation and as stipulated by HSA.

[2] An example of an innovative salvage therapy, in relation to In-House Manufactured CTGTPs, is the administration of non-registered In-House Manufactured CTGTP(s) to a patient where the quality, safety and efficacy of the In-House Manufactured CTGTP(s) has/have not been ascertained and/or verified by HSA, and where the patient has a refractory disease of which first and second-line treatment options have failed, and the In-House Manufactured CTGTP(s) is/are administered as a last resort.

CTGTPs in Research / CT; and the requirements set out in paragraph 5 of these LCs shall apply to the use of In-House Manufactured CTGTPs in innovative salvage therapy.

A. Information to be provided before taking appropriate / informed consent

3.3 The Licensee shall ensure that the patient, research / clinical trial subject, or person authorised to give consent[3] (as the case may be) has minimally been informed of the following, prior to appropriate / informed consent[4] being taken for the Generally Accepted Treatment, Research / CT, or innovative salvage therapy (as the case may be; and in this paragraph 3.3 referred to as the "**Intervention**") involving the use of In-House Manufactured CTGTP(s):

(1) the purpose of the Intervention and use of CTGTP[5] in the Intervention;
(2) the nature of the Intervention and related follow-up procedures, if any (e.g., whether the patient would require long-term special care, or other medications);
(3) that the CTGTP is an In-House Manufactured CTGTP;
(4) the manufacturing method of the CTGTP and potential outcomes (e.g., varying quality, efficacy or quantity that may be expected);
(5) where applicable, that the CTGTP is not registered with HSA and that its quality, safety and efficacy have not been evaluated on a scale comparable to commercially available products;
(6) whether the CTGTP is approved by any other regulatory authority and the indication(s) for which is it approved for clinical use;
(7) possible benefits of the Intervention using the CTGTP that are supportable with scientific evidence, and when the benefits would be expected to appear and be measured;
(8) known and potential risks that are material to the patient or research / clinical trial subject (as the case may be) in his/her particular circumstances, including reported adverse events related to the CTGTP;
(9) details of costs or potential costs to be borne by the patient or research / clinical trial subject (as the case may be), and possible sources of financial assistance (if any)[6];

[3] Such as a donee or deputy authorised to give consent for a patient or research / clinical trial subject lacking mental capacity, pursuant to the Mental Capacity Act 2008.

[4] Licensees are reminded that the taking of appropriate / informed consent must also be carried out in accordance with all relevant requirements, including applicable legal (such as those under the Human Biomedical Research Act 2015) and professional (such as those under the SDC/SMC ECEG) requirements.

[5] References to "CTGTP" in this paragraph 3.3 refers to the In-House Manufactured CTGTP(s) to be used in the Intervention.

[6] For innovative salvage therapies, Licensees should only charge what patients would have paid for if they had undergone comparable conventional or palliative treatments. Licensees are reminded that the charging of research subjects is not allowed.

(10) where applicable, reason(s) why alternative treatments are of no avail, or are unlikely to be effective;
(11) where applicable, alternative research options, if any;
(12) plans for long-term monitoring / follow up after the Intervention, if any (including the need for long-term submission of patient outcome data to MOH for innovative salvage therapies); and
(13) how and for how long the patient's or research / clinical trial subject's personal data (as the case may be) will be used and stored.

B. Appropriate systems

3.4 The Licensee shall ensure that it has appropriate systems (including appropriate clinical set-ups in its HCI(s)) in place to manage serious adverse events ("**SAEs**")[7], relating to the use of In-House Manufactured CTGTPs, effectively (e.g., management of cytokine release syndrome, immunoglobulin replacement, and availability of antidotes).

3.5 The Licensee shall ensure that it has appropriate systems in place to enable long-term follow-up, for a period of at least 15 years, of patients for delayed SAEs which may develop, relating to the use of In-House Manufactured CTGTPs (e.g., malignancies for CTGTPs that involve viral vectors).

C. Record keeping

3.6 The Licensee shall establish appropriate mechanisms to ensure that the In-House Manufactured CTGTP and its raw materials, including all substances that come into contact with human cells/tissues, is traceable to the patient, research / clinical trial subject and/or donor (as applicable), and at all stages in the process of their sourcing, manufacturing, packaging, storage, transportation and delivery.

3.7 The Licensee shall keep all such records (mentioned in paragraph 3.6) to facilitate traceability to the patient, research / clinical trial subject and/or donor (as applicable) for a period of at least 30 years after the expiry of the In-House Manufactured CTGTP.

[7] A 'serious adverse event' is an adverse event that:
(a) may result in a person's death;
(b) may threaten a person's life;
(c) results in a person being hospitalised or prolongs a person's existing stay in hospital;
(d) results in a person's persistent or significant disability or incapacity;
(e) results in a congenital anomaly or birth defect; or
(f) is medically important even though the effect may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the person's health or may require intervention to prevent the person's death or one of the other outcomes mentioned in (c), (d) and/or (e) above.

3.8 The Licensee shall ensure that all such records (mentioned in paragraph 3.6) are kept in a readily accessible database, and shall facilitate any ad-hoc audits or inspections of the database by the Director-General of Health and/or officers from MOH.

4 Additional requirements for use of In-House Manufactured CTGTPs in Research / CT

4.1 The Licensee shall ensure that its Research / CT involving In-House Manufactured CTGTPs complies with all relevant legal requirements, including those imposed under the applicable provisions of the Human Biomedical Research Act 2015 and the Health Products (Clinical Trials) Regulations 2016.

5 Additional Requirements for use of In-House Manufactured CTGTPs in innovative salvage therapy

A. Notification to MOH

5.1 In relation to innovative salvage therapy, the Licensee shall notify MOH of its intent to:

(1) manufacture and/or process In-House Manufactured CTGTP(s)[8]; and
(2) administer the In-House Manufactured CTGTP(s),

by completing and submitting Form A-1[9] to MOH at least 24 hours prior to the manufacturing and/or processing of the In-House Manufactured CTGTP(s).

5.2 When submitting its completed Form A-1, the Licensee shall also submit the following documents to MOH:

(1) approvals / agreements from the relevant committees / authorities mentioned in paragraphs 5.4 and 5.5; and
(2) signed consent forms.

5.3 The Licensee shall not administer the In-House Manufactured CTGTP to the patient in the innovative salvage therapy until all requirements in paragraphs 5.1 and 5.2 are fulfilled.

B. Approvals from relevant committees / authorities

[8] Including if the In-House Manufactured CTGTP will be manufactured by another HCI or a third-party commercial entity; see the definition for "In-House Manufactured" at paragraph 2.1(3).
[9] Form A-1 is to be submitted at: https://form.gov.sg/5e295d403acc0e001141bcbe.

5.4 The Licensee shall ensure that, prior to the administration of In-House Manufactured CTGTP(s) in innovative salvage therapy, approval / agreement have been obtained from the following committees / authorities on the same:

(1) The HCI's[10] tumour board, or specialty board for that particular disease / condition, or at least two medical practitioners qualified to confirm the patient's need for the innovative salvage therapy (involving the administration of the In-House Manufactured CTGTP(s)) as a last resort (e.g., due to the ineffectiveness or unsuitability of current conventional therapy) and who are independent of the patient's treatment team; and

(2) a Clinical Ethics Committee (CEC).

5.5 The Licensee shall also ensure that other necessary approvals / agreements, such as from the National Environment Agency, Genetic Modification Advisory Committee, and/or MOH's Biosafety Branch, are obtained, where relevant.

C. Reporting of serious adverse events

5.6 The Licensee shall ensure that all SAEs are reported as soon as possible, and in any event no later than seven calendar days from the Licensee's first knowledge that a case qualifies as an SAE, to HSA at https://go.gov.sg/AEreporting.

D. Submission of data to MOH

5.7 The Licensee shall ensure that the following data are tracked, reviewed and submitted to MOH in relation to each patient's innovative salvage therapy, for MOH's safety monitoring and future cost-effectiveness studies (through Form A-2[11]):

(1) patient profile;
(2) particulars of the In-House Manufactured CTGTP(s) used;
(3) mode and site of administration of the In-House Manufactured CTGTP(s);
(4) dosage and administration of the In-House Manufactured CTGTP(s);
(5) quality attributes (e.g., identity, purity, impurity, viability, sterility, potency) of the In-House Manufactured CTGTP(s);
(6) clinical outcomes (e.g., response, relapse, remission);
(7) adverse outcomes / SAEs (e.g., death, cytokine release syndrome, infection, secondary tumour or other adverse events that may be of significance), if any;

[10] The Licensee's HCI that will be carrying out the innovative salvage therapy.

[11] Form A-2 may be found at: https://form.gov.sg/5e32869e0ec75e0011f2928c. Form A-2 must be submitted for each patient's innovative salvage therapy as specified, unless data collection is no longer feasible, e.g., in the event of patient death.

(8) follow-up period, if any;
(9) patient-reported outcome (e.g., health-related quality of life data); and
(10) cost (e.g., manufacturing cost of the In-House Manufactured CTGTP(s), cost for monitoring, cost of treating SAEs).

5.8 The Licensee shall complete and submit Form A-2 in 3-monthly intervals (i.e., submission every 3 months) after the administration of the In-House Manufactured CTGTP(s) for the 1st year, 6-monthly intervals for the 2nd year, and yearly intervals from the 3rd year onwards for a period of at least 15 years.