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KEMENTERIAN KESIHATAN MALAYSIA

GUIDELINES
ON STEM CELL AND CELL-BASED RESEARCH AND THERAPY

3RD EDITION

MEDICAL DEVELOPMENT DIVISION

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ON STEM CELL AND CELL-BASED RESEARCH AND THERAPY

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was developed by

National Committee on Ethics of Cell Research and Therapy (NCERT)

in collaboration with

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FOREWORD

DIRECTOR-GENERAL OF HEALTH MALAYSIA

The primary goals of stem cell and cell-based research are to advance scientific understanding, to generate evidence for addressing unmet medical and public health needs, and to develop safe and efficacious therapies for patients. Scientific breakthroughs and technological advances in the field of stem cell have grown rapidly in the past decades with advancements of stem cell research and therapy into the realm of gene therapy.

Parallel to these scientific developments, responsible and ethical research must focus on harnessing the potential of science to improve our understanding of human health and illness, as well as discover newer ways to prevent and treat illness.

The updated Guidelines on Stem Cell and Cell-Based Research and Therapy 3rd edition is a timely review since its second publication in 2009. This guideline promotes ethical, practical, and appropriate enterprise for stem cell research and development of new therapies to improve human health and well-being.

This guideline will guide researchers and clinicians for a better and systematic approach to conduct research and therapies to ensure ethical research of the highest quality and no harm is done to the patients. Failure to do so may result in repercussions which may put the practitioners or scientists in a difficult position especially if they are proven to be unethical in their practice or research with regards to the use of stem cells. I hope this guideline will be a valuable reference document to clinicians, researchers, institutional research, and ethics committee as well as the public.

DATUK DR MUHAMMAD RADZI BIN ABU HASSAN
Director-General of Health Malaysia

FOREWORD

DEPUTY DIRECTOR-GENERAL OF HEALTH (MEDICAL) MALAYSIA

Stem cell and cell-based research have advanced tremendously within the past two decades producing new technologies and treatment methods with the likes of cellular therapy and gene therapy. The principal and spirit of stem cell and cell-based research have always been to find new ways to cure previously untreatable disease and ameliorate the lives of patients and their family.

With the advancement of new technologies and therapies comes new challenges of maintaining the ethical standards as well as the safety and quality of new treatment modules. While it is important to promote scientific breakthroughs in cellular research and therapy, ethics and safety of patients maintains to be paramount in this endeavour. Rapid developments in this scientific field warrants and justifies the update of Guidelines on Stem Cell and Cell-Based Research and Therapy which was last reviewed back in 2009.

The National Guidelines for Stem Cell and Cell-Based Research and Therapy 3rd Edition is hoped to guide scientists and clinicians in their effort to produce new knowledge which would later be translated into clinical therapies in an ethical and safe manner. I would like to congratulate and commend the outstanding work of the committee and all parties involved for producing this guideline. May it be a valuable reference and source of information for all scientists, clinicians and as well as for the public.

DATO' INDERA DR NOR AZIMI BINTI YUNUS
Deputy Director-General of Health (Medical) Malaysia

FOREWORD

CHAIRMAN NATIONAL COMMITTEE IN ETHICS OF CELL RESEARCH AND THERAPY (NCERT)

In the ever-evolving landscape of stem cell and cell-based research, the primary commitment of NCERT remains steadfast: advancing scientific understanding, educating researchers on the need for robust scientific research approach as well as fostering ethical practices in cell research and therapy to improve human health.

The Guidelines for Stem Cell and Cell-Based Research and Therapy, now in its 3rd edition, is timely indeed. This was developed via a stakeholders approach and also input and comments by the top experts in the field of stem cell and cell research and therapy. Clear ethical principles are highlighted in the relevant chapters together with practical insights directing researchers and clinicians towards a path of responsible research and patient-centred care. The guidelines outlined within this document provide a framework for conducting research and therapies with integrity, ensuring the highest standards of quality and safety for patients.

I would like to thank all the members of NCERT, all the contributors to each of the chapters, all the editors who helped edit the document and to the members of the secretariat at the Ministry of Health Malaysia.

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ABBREVIATIONS & ACRONYMS

AE	Adverse Event
ART	Assisted Reproductive Technology
CAR T	Chimeric antigen receptor (CAR) T
CCBP	Cell and Cell-Based Product
CDCR	Control of Drugs and Cosmetics Regulation
CGTPs	Cell And Gene Therapy Products
CKAPS	Private Medical Practice Control Section
CTIL	Clinical Trial Import License
CTPs	Cell Therapy Products
CTs	Clinical Trials
CTX	Clinical Trial Exemption
EMA	European Medicines Agency
FIH	First-In-Human
DNA	Deoxyribonucleic Acid
DRGD	Drug Registration Guidance Document
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTP	Good Tissue Practice
GVHD	Graft-versus-Host Disease
hES	Human Embryonic Stem
HSCs	Haematopoietic Stem Cells
IEC	Institutional Ethics Committee
IP	Investigational Product
ISSCR	International Society for Stem Cell Research
NK	Natural Killer
MAD	Multiple Ascending Dose
MDA	Medical Device Authority

MHC	Major Histocompatibility Complexes
MOA	Mechanism of Action
NCERT	National Committee on Ethics of Cell Research and Therapy
NMRR	National Medical Research Register
NOAEL	No-Observed Adverse Effect Level
NPRA	National Pharmaceutical Regulatory Agency
OECD	Organisation for Economic Co-Operation and Development
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PD	Pharmacodynamic
POC	Proof-of-Concept
PI	Principal Investigator
RMP	Risk Management Plan
SAD	Single Ascending Dose
SCNT	Somatic Cell Nuclear Transfer
SVF	Stromal Vascular Fraction
US-FDA	US-Food and Drug Administration
VICH	Veterinary International Conference on Harmonization
3R	Replacement, Reduction and Refinement

1.0

SCOPE OF CELLS FOR RESEARCH AND THERAPY

1.0 SCOPE OF CELLS FOR RESEARCH AND THERAPY

1.1. Introduction

Although there are many controversies surrounding stem cell research and therapies, the Ministry of Health Malaysia recognises that it is crucial for local scientists and clinicians to be involved in stem cell research provided that these conform to ethical guidelines. Stem cell and cell therapy still hold a lot of promises and could potentially deliver innovative therapies in many different diseases. It is vital for medical scientists to keep abreast of current advances in science, especially when there is an enormous potential of revolutionizing therapy in the form of cell replacement therapy. Within cell therapy, there are different types of cells involved. This chapter addresses the scope and the variety of cells within cell therapy that are regulated by the Ministry of Health Malaysia.

1.2. The Status of Stem Cell Research in Malaysia

Stem cell research has been increasing in Malaysia involving both government and private institutions. Most of the research thus far has involved haemopoietic stem cells (bone marrow, peripheral blood, cord blood and mesenchymal stem cells). As these are from adult tissues, ethical concerns may be minimal since they are being used in the setting of haemopoietic stem cell transplantation. The use of sources of cells other than the adult stem cells e.g. cell lines or fertilized embryos is a major concern as it is likely that our local researchers could be conducting research in this area.

1.3. Cell Research and Therapy

Cell therapy is defined as the administration of living whole cells to a patient for the treatment of a disease. The origin of the cells can be from the same individual (autologous source) or from another individual (allogeneic source).

Historically, blood transfusions were the first type of cell therapy and are now considered routine. Bone marrow transplantation has also become a well-established medical treatment for many diseases, including cancer, immune deficiency, and others.

Cell therapy is expanding its repertoire of cell types for administration. Cell therapy treatment strategies include: isolation and transfer of specific stem cell populations, administration of effector cells and infusion of embryonic stem cells or induced pluripotent stem cells.

Studies have also been performed for treatment that combines the technologies of gene and cell therapy.

Gene therapy is the introduction, removal, change or edit in the content of a person's genetic code with the goal of treating or curing a disease. Moreover, it is a set of strategies that modify the expression of an individual's genes or repair abnormal genes. Combination of cell and gene therapy has been applied in clinical setting such as the use of Chimeric antigen receptor (CAR) T-cell therapy in some leukaemias and lymphomas.

1.4. Scope of Cells

The scope of cells in this guideline shall include stem cells and other cells involved in cell and gene therapy research.

Stem cells can be categorised according to self-renewal and differentiation properties as either pluripotent stem cells, multipotent stem cells or unipotent stem cells.

1.4.1. **Pluripotent stem cells** can give rise to all cell types. Examples of pluripotent stem cells include embryonic stem cells and induced pluripotent stem cells.

1.4.2. **Multipotent stem cells** have the capacity to self-renew by dividing and to develop into multiple specialised cell types present in a specific tissue or organ. Most adult stem cells including haemopoietic stem cells and mesenchymal stem cells are multipotent stem cells.

1.4.3. **Unipotent stem cell** are cells that are capable of differentiating along only one cell type. Also, it may be that the adult stem cells in many differentiated, undamaged tissues are typically unipotent and give rise to just one cell type under normal conditions. This process would allow for a steady state of self-renewal for the tissue.

1.4.4. **Other cell types** that are used in cell therapy include T-lymphocytes, natural killer cells, dendritic cells, islet cells, chimeric antigen receptor (CAR) T-cell and other cells. The cells are usually either effector cells or antigen presenting cells that are capable of mounting immune response against certain diseases and cancers. Pancreatic islet cells are the cluster of cells that produce insulin, gastrin, glucagon and somatostatin. CAR T-cell therapy is also sometimes referred to as a type of cell-based gene therapy, because it may involves altering the genes inside T cells to help them attack the cancer cells.

1.5. Stem Cell Type, Technologies and Research Recommendation

No.	Cell Type	Definition	Current Indication / Suggested Recommendation
1.	**Human Embryonic Stem Cells (HESC)**	HESC are pluripotent stem cells from the embryo. Somatic cell nuclear transfer is a laboratory technology for creating a viable embryo from a body cell and an egg cell. The technique consists of taking anucleated oocyte (egg cell) and implanting a donor nucleus from a somatic (body) cell.	Human Embryonic Stem Cells research is generally a **restrictive** research area. Previously it is limited to donated surplus embryo of less than 14 days. But on 26 May 2021, the International Society for Stem Cell Research (ISSCR) is relaxing this prominent limit of 14-day rule. The ISSCR now suggests that studies proposing to grow human embryos beyond 14 days to be considered on a case-by-case basis and be subjected to several phases of review to determine at what point the experiments must be stopped. Research is **prohibited** if it involves creation of human embryos for the sole aim of research, reproductive cloning, embryos beyond 14 days and creation of chimera of animal fusion.
2.	**Induced Pluripotent Stem Cells (IPSC)**	IPSC are reprogrammed pluripotent stem cell from somatic cells. Common somatic cell sources are fibroblast from skin and blood cell (mononuclear cells and lymphocytes).	Induced pluripotent Stem Cells shall be a **restrictive** research area. Example of research area that have been conducted includes disease modelling and therapeutic screening, drug screening, patient specific cell-based therapy and cell-based regenerative medicine.

No.	Cell Type	Definition	Current Indication / Suggested Recommendation
		There are many technologies involved in the induction pluripotent stem cells from adult cells which include somatic cell technologies, cell immortalisation technologies, ex-vivo gene modification of cells using viral vector technologies, genome editing technologies, cell plasticity technologies, 3D/ tissue engineered products including encapsulated cells technologies and any combination of the above methods.	There are currently a lot of interest in generating IPSC from adult cells of patients with different diseases to help in deeper understanding of disease pathology.
3.	**Hematopoietic Stem Cells (HSCs)**	HSCs are multipotent stem cells that can give rise to different matured blood cells. Sources of hematopoietic stem cells include peripheral blood, bone marrow and cord blood. There are many technologies involved in hematopoietic stem cells research which include somatic cell technologies, cell immortalisation technologies, ex-vivo gene modification of cells using viral vector technologies, genome editing technologies, cell plasticity technologies, 3D technologies and any combination of the above methods.	Hematopoietic stem cells transplantation is a standard treatment in a number of haematological diseases. It is a **permissive** research area in solid tumours and auto immune diseases but shall be a **restrictive** research area in neurological disorders, cardiology, urology and sport medicine. Direct infusion of allogenic cord blood for regenerative medicine shall be **prohibited**.

No.	Cell Type	Definition	Current Indication / Suggested Recommendation
4.	**Mesenchymal Stem Cells (MSC)**	MSC belong to another type of multipotent stem cells. In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed minimal criteria to define human mesenchymal stem cell. First, mesenchymal stem cell must be plastic-adherent when maintained in standard culture conditions. Second, it must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules. Third, it must differentiate to osteoblasts, adipocytes and chondroblasts in vitro. Human mesenchymal stem cells were first identified in the bone marrow and are alternatively known as "mesenchymal stromal cells."	Mesenchymal stem cell research and therapy is **permissible** in steroid refractory acute Graft-versus-host disease (GVHD). The treatment has been accepted as a standard treatment in New Zealand and Canada for the above condition. Mesenchymal stem cell research shall be a **restrictive** research area in other indications than the above, including neurological disorders, cardiovascular diseases, urological disorders, orthopaedics and sport medicine disorders as well as regenerative medicine. For the above conditions, researchers should embark on pre-clinical trials (using the appropriate animal model) followed by clinical trials.

No.	Cell Type	Definition	Current Indication / Suggested Recommendation
		However, mesenchymal stem cell has since been shown to be derived from nearly all tissues. The technologies involved in mesenchymal stem cell research are somatic cell technologies, ex-vivo gene modification of cells using viral vector, genome editing, cell plasticity technologies: regenerative medicine, 3D technologies and any combination of above methods.	
5.	**Tissue Specific Stem Cells**	These are unipotent stem cells derived from specific tissue, for example: specific skin, muscle, vascular, limbal, and cardiac stem cells. Technologies involve in tissue specific stem cells research are somatic cell technologies, isolation and expansion under Good Manufacturing Practice (GMP) facility, 3D technologies or any combination of above methods.	Tissue specific stem cell research shall be a **restrictive** research area.

1.6. Other Cell Type, Technologies and Research Recommendation

1.6.1. **T lymphocytes** are so called because they are predominantly produced in the thymus. There are two major types of T cells: the helper T cell and the cytotoxic T cell. T cell receptors on T lymphocytes recognize the major histocompatibility complexes (MHC) on antigen presenting cells. There are two types of MHC: MHC class I and MHC class II. MHC class I presents to cytotoxic T cells; MHC class II presents to helper T cells. T lymphocytes infusion is a standard treatment in haemopoietic stem cell transplantation.

Technologies involved in T lymphocytes research include somatic cell technologies in adoptive antigen specific T cell engineering, expansion of T cell subtypes, cell immortalisation technologies in residual memory T cell, ex-vivo gene modification of cells using viral vector technologies in Chimeric antigen receptor T-Cell (CAR-T), genome editing technologies in CAR-T, cell plasticity technologies in expansion of T cell subtypes and in any combination of above methods.

Recommendation for research:

Chimeric antigen receptor (CAR) T cells are a type of T lymphocytes that have been engineered to express a specific CAR, which programs them to effectively target an antigen on tumours and thus they destroy the tumour cells directly bypassing MHC restricted pathway. The receptors are chimeric because they combine both antigen-binding and T-cell activating functions into a single receptor. CAR-T cells are engineered to be specific to an antigen expressed on a tumour.

CAR-T cell therapy for refractory B- cell malignancies shall **be permissible**. US-Food and Drug Administration (US-FDA) has approved CAR T for treatment of refractory B cell malignancies. T lymphocytes research shall be a restrictive research area in other indications than stated above.

1.6.2. **Natural killer (NK) cells** are a type of cytotoxic lymphocyte of the innate immune system. NK cells are unique as they have the ability to recognise diseased cells in the absence of antibodies and MHC, allowing for a much faster immune reaction. Technologies involved in NK cells research include somatic cell technologies with minimally manipulative NK cell expansion, ex-vivo gene modification of cells using viral vector technologies, genome editing technologies and any combination of the above methods.

Recommendation for research:

Natural Killer cells research shall be a **restrictive** research area.

1.6.3. **Dendritic cells** are antigen presenting cells. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. Technologies involved in dendritic cells research include somatic cell technologies with minimally manipulative NK cell expansion, ex-vivo gene modification of cells using viral vector technologies, genome editing technologies and any combination of the above methods.

Recommendation for research:

Dendritic cells research shall be a **restrictive** research area.

1.7. Animal Cells Research

Usage of animal cells as a source for clinical use shall be **prohibited**.
However, these cells are only permissible in research involving animal recipients.

Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of either:

(a) live cells, tissues or organs from a non-human animal source, or

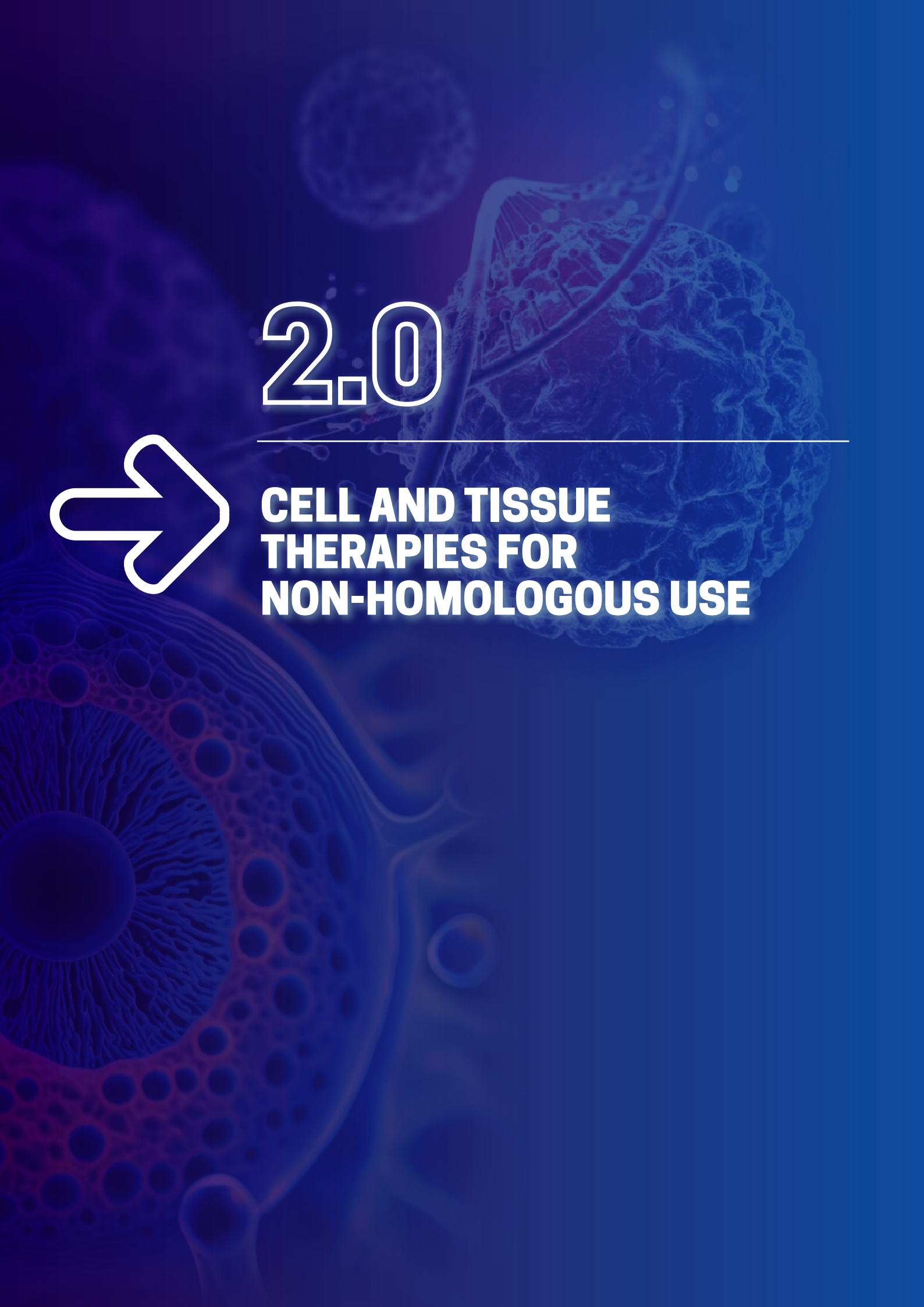
(b) human body fluids, cells, tissues or organs that have ex vivo contact with live non-human animal cells, organs or tissue.

Human-animal stem cells chimera is an organism carrying cell populations derived from two different stem cells of different species.

Recommendation for research:

Xenotransplantation and human-animal stem cells chimera research shall be a **restricted** research area. The process of research should be over-sighted and very closed monitored by an independent body.

Animal chimera incorporating human cells with the potential to form human gametes shall be **strictly prohibited**.



2.0

CELL AND TISSUE THERAPIES FOR NON-HOMOLOGOUS USE

2.0 CELL AND TISSUE THERAPIES FOR NON-HOMOLOGOUS USE

2.1. Introduction

Cell and tissue therapies have become an inevitable arm of modern medicine as many diseases that were once considered as terminal could now be treated. The advancement of these therapies has been of considerable interest to many stakeholders due to their unique characteristics and properties which had enabled them to be recognised as an attractive treatment option especially for fatal or incurable diseases.

Cells and tissues that are notably manipulated or used in a non-homologous manner must be proven safe and effective for the intended use before being offered to patients or integrated into standard clinical care.

An introduction to non-homologous use for cell and tissue therapy is described in this chapter to facilitate all stakeholders. The guidelines discussed here shall be adhered to all healthcare providers involved in the provision of the treatment to patients.

2.2. Cell and Tissue Therapy Strategies

Cell and tissue therapy utilise autologous, allogeneic or xenogeneic sources which may involve genetic engineering or manipulation formulations transferred into a patient for medical purpose.[3,4]

2.2.1. **Autologous**: Cells/tissues derived from a patient and returned to the same patient after in vitro manipulation.

2.2.2. **Allogeneic**: Cells/tissues derived from donors and the final cell therapy can be used to treat many different patients.

2.2.3. **Xenogeneic**: Cells/tissues derived from nonhuman animal source into a human recipient through transplantation, implantation or infusion.

2.3. Non-homologous Use of Cell and Tissue Therapy

Non-homologous use of cell and tissue therapy is defined as repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues that perform a different basic functions in the recipient as in the donor.

Examples of non-homologous use of cell and tissue therapy:

2.3.1. Using haematopoietic stem cells (HSCs) from bone marrow infused into an artery with a balloon catheter for the purpose of limiting ventricular remodelling following acute myocardial infarction. This is non-homologous use because limiting ventricular remodelling is not a basic function of bone marrow.

2.3.2. Using HSCs derived from cord blood with a package insert stating that cord blood may be infused intravenously to differentiate into neuronal cells for treatment of cerebral palsy. This is not homologous use because there is insufficient evidence to support that such differentiation is a basic function of these cells in the donor.

2.3.3. Using xenogeneic porcine pancreatic islet cells, hepatocytes and neuronal cells as a living drug for the treatment of degenerative and organ failure diseases.[4]

2.3.4. Using an adipose-derived mesenchymal stromal cell for delivering into the eye with the intent to treat macular degeneration. This is a non-homologous use because the basic function of adipose tissue is not the trophic support of the retina.[5]

2.3.5. Using platelet-rich plasma and derivatives for improvement of wound healing outcome. This is a non-homologous use because the basic function of platelet is to stimulate coagulation factors and other mediators to achieve hemostasis.[6]

2.3.6. Minimal manipulation is a phrase often referred to stem cells with respect to assigning regulatory requirements in the clinical applications. Cells that are minimally manipulated are classified as Class I. The US-Food and Drug Administration (US-FDA) defines minimal manipulation as:

i. For structural tissue: processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and

ii. For cells or non-structural tissues: processing that does not alter the relevant biological characteristics of cells or tissues.

2.3.7. Use of Stromal Vascular Fraction (SVF) for non-homologous use are subject to regulation if they are processed, used for purposes that are not their normal function, also known as "non-homologous use," combined with non-tissue materials, or used for metabolic purposes, as per the US-Food and Drug Administration regulation.

2.4. Regulatory Requirements

Cell and tissue therapy for non-homologous use, are classified under Class II. A Class II product is “highly processed”, used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes”. It is regulated as a biologic product by the National Pharmaceutical Regulatory Agency and Medical Device Authority (NPRA), Ministry of Health Malaysia.

3.0

“PRE-CLINICAL TESTING” (OR NON-CLINICAL TESTING) RECOMMENDATIONS FOR ADVANCED THERAPEUTICS (COVERING CELL AND GENE THERAPIES)

3.0 "PRE-CLINICAL TESTING" (OR NON-CLINICAL TESTING) RECOMMENDATIONS FOR ADVANCED THERAPEUTICS (COVERING CELL AND GENE THERAPIES)

3.1. Introduction

Pre-clinical (or non-clinical testing) of medicinal products under this guideline is specifically meant for products to be used in humans. It is conducted to support clinical trials and marketing authorisation applications involving the use of cells and tissue(s) (or its derivatives) of all types. Medicinal product regulatory testing is also conducted to control quality during (in-process) and/or at the end (final product batch testing) of the production of the medicinal product. To comply with NPRA directives, associated guidelines, and various regulations, quality, non-clinical and target animal safety and efficacy testing can require the use of animals for the development of human medicinal products. It is important to note that in addition to human ethical implications, ethical and animal welfare considerations demand that animal use be limited and preferably avoided as much as possible.

The primary goals of pre-clinical safety evaluation are:

1. to identify an initial safe dose and subsequent dose escalation schemes in humans;
2. to identify potential target organs for toxicity and/or efficacy; and
3. to identify safety parameters for clinical monitoring.

Adherence to the principles presented in this document is intended to improve the quality and consistency of the pre-clinical safety data supporting the development of Medicinal Products derived or related to cells.

In this document, the scope of "Medicinal Products" is defined and described within sub-section 3.2 (Scope).

This guideline serves as the guidance document that governs and direct the conduct of the use of humans as well as animals (as a whole organism or, in part, produced/extracted/processed/derived samples) in pre-clinical testing methods. It covers both the testing under in vitro and in vivo conditions, and in the latter, it unambiguously fosters the application of the principle of the 3Rs (Replacement, Reduction and Refinement) when selecting the method of choice.

3.2. Scope

For the purpose of this guidelines or guidance document, "Medicinal Product" is defined as the product(s) that is/are derived from any source that is associated with cells (inclusively) either as a whole or in part, and used in whatever method or technique under any conditions to be used in human for various purposes such as but not limited for use in treatment, wellness or prevention of disease.

This guideline applies to requirements to support regulatory applications for:

3.2.1. Non-clinical testing and non-human trials (*both in vitro and in vivo*) during the development of medicinal products that uses cells of all types, either in part, whole or extracted/processed/derived from these cells.

3.2.2. Experiments or studies that are involved using cells mentioned above involving animal as well as human sources either in part or whole, including but not limited to cells or tissues, protein, genetic or other biological aspects related to these, to develop medicinal products.

3.2.3. Quality batch control as part of the manufacturing process of medicinal products (in-process and/or final product batch testing).

This guideline is intended primarily to recommend a basic framework for the pre-clinical safety and efficacy evaluation of cells, cell-derived or related medicinal products. It applies to products derived from characterised cells through various expression systems, including bacteria, yeast, insect, plant, and mammalian cells. The active substances include proteins and peptides, their derivatives and products of which they are components; they could be derived from cell cultures or produced using recombinant DNA technology, including production by transgenic plants and animals. Examples include but are not limited to: cytokines, plasminogen activators, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, exosomes, spheroids, organoids and monoclonal antibodies. The intended indications may include in vivo diagnostic, therapeutic, or prophylactic uses.

The principles outlined in this guidance may also apply to recombinant DNA protein vaccines, chemically synthesised peptides, plasma-derived products, endogenous proteins extracted from human tissue, and oligonucleotide drugs.

This document does not cover antibiotics, allergenic extracts, heparin, vitamins, conventional bacterial or viral vaccines, or DNA vaccines.

3.3. General Principles

When conducting pre-clinical testing, studies must consider the following:

3.3.1. The selection of the relevant animal species including the appropriate disease model.

3.3.2. The appropriate age of the animal that represents the target human therapeutic population.

3.3.3. The physiological state of the animal model.

3.3.4. The manner of the developed medicinal product to be delivered, including dose, route of administration, and treatment regime to be used.

3.3.5. The test material's stability under the conditions it is to be used.

Safety (or toxicity) studies (where indicated and justified by the applicant) are expected to be performed in compliance with Good Laboratory Practice (GLP). The facilities and standards should meet the OECD standards. For example, in the use of pluripotent stem cells, teratogenic studies would need to be determined but are not applicable for use involving mesenchymal stem cells. It is to be considered that in certain studies and circumstances where there is a need to employ specialised test systems that are not offered under GLP standards or nationally, these can be exempted with good reasons. Nevertheless, parts that do not comply with these standards need to be identified and considered, although these do not constitute data to be used to support clinical trials and marketing authorisations.

3.4. Legal & Regulatory basis

This guideline must be read in conjunction with:

3.4.1. Guidelines for Stem Cell Therapy. MOH/P/PAK/177.08(GU). ISBN 978-983-3433-63-6

3.4.2. Malaysia Animal Welfare Act 2015 (Act 772)

3.4.3. Guidance Note for Cell and Gene Therapy Products Guidelines (CGTP). NPRA. 2016/2021

3.5. Rationale for conducting pre-clinical studies

The main rationale for conducting pre-clinical studies is meant mainly, but not exclusively, for the following reasons:

3.5.1. To demonstrate the safety and/efficacy of the Medicinal Product as an indicator for human use.

3.5.2. To establish a "proof-of-concept" (POC) model that would dictate and indicate how, where, when and/or how much of the Medicinal Product is to be used in humans.

3.5.3. To establish the baseline data and mechanistic features of the mechanism of action (MOA) from the Medicinal Product.

3.5.4. To generate data that would be required to support legal use, product registration, accreditation, clinical trials data or product marketing approvals (and other related uses that may be related or similar to those mentioned above).

3.5.5. Where possible and/or necessary, the demonstration of cellular bio-distribution following the introduction of cells in the animal.

In addition to using the principles of 3R as stated, the institutional animal care and use committee needs to approve any studies that involve the use of animal cells or its derivative. In studies using human cells, these need to adhere to and meet the approval of the national or local research ethics committee.

3.6. Consideration for pre-clinical study designs

3.6.1. In designing and selecting the best pre-clinical study to be conducted in line with the appropriate research question to be answered to develop a cell-based/derived medicinal product, selected outcome parameters must first be established. These may include (but are not limited to) the following:

3.6.1.1. Biological activity (Or Pharmacokinetics): These may be evaluated using *in vitro* assays or animal serum levels following *in vivo* experiments to determine which effects of the product may be related to clinical activity. The use of cell lines and/or primary cell cultures can be useful to examine the direct effects on cellular phenotype and proliferation. The combined results from *in vitro* and *in vivo* studies assist in the extrapolation of the findings to humans. In vivo studies to assess pharmacological activity, including the defining mechanism(s) of action, are often used to support the rationale of the proposed use of the product in clinical studies.

3.6.1.2. Dose and administration route selection: The route and frequency of administration should be as close as possible to that proposed for clinical use. Consideration should be given to the pharmacokinetics and bioavailability of the product in the species being used, and the volume which can be safely and humanely administered to the test animals. For example, the frequency of administration in laboratory animals may be increased compared to the proposed schedule for human clinical studies to compensate for faster clearance rates or low solubility of the active ingredient. In these cases, the level of exposure of the test animal relative to the clinical exposure should be defined. Consideration should also be given to the effects of volume, concentration, formulation, and administration site. The use of routes of administration other than those used clinically may be acceptable if the route must be modified due to limited bioavailability, limitations due to the route of administration, or to size/physiology of the animal species. Dosage levels should be selected to provide information on a dose-response relationship, including a toxic dose and a no-observed adverse effect level (NOAEL).

3.6.1.3. Immunogenicity: Measuring antibody levels associated with administering medicinal products should be performed when conducting repeated dose toxicity studies. These data are meant to assist in the interpretation of preclinical studies. Antibody responses should be characterised (e.g., titre, number of responding animals, neutralising or non-neutralising), and their appearance should be correlated with any pharmacological and/or toxicological changes. Specifically, the effects of antibody formation on pharmacokinetic/pharmacodynamic parameters, incidence and/or severity of adverse effects, complement activation, or the emergence of new toxic effects should be considered when interpreting the data.

3.6.1.4. Toxicity: Measuring levels of various toxicity can be performed by direct or indirect measures, including biological markers such as serum levels of toxic content. Routine toxicology parameters should continue to be evaluated (e.g: serum chemistry panel haematology) in addition to other biomarkers relevant to your specific therapy type. For example, in a gene-modified stem cell, the expressed transgene levels and/or activity may be useful Pharmacodynamic (PD) marker in toxicology studies. In cases where toxicity cannot be measured directly, other monitoring methods, such as determining the changes in organ function, may be used as an indicator of toxicity.

3.6.2. It is paramount that a "fit-for-purpose" pre-clinical study design has to be employed at all times. These may include and are not limited to the following:

3.6.2.1. Appropriate animal model selection: The biological activity, species, and/or tissue specificity of many biotechnology-derived pharmaceuticals often preclude standard toxicity testing designs in commonly used species. Animals may include large or small, and the selection of these relates to the pathology of the disease model rather than the source of cells. Toxicity studies in non-relevant species may be misleading and discouraged. When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered. The information gained from using a transgenic animal model expressing the human receptor is optimised when the interaction of the product and the humanised receptor has similar physiological consequences to those expected in humans.

3.6.2.2. Relevant models: Toxicity studies in non-relevant species may be misleading and discouraged. When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered. The information gained from using a transgenic animal model expressing the human receptor is optimised when the interaction of the product and the humanised receptor has similar physiological consequences to those expected in humans.

3.6.2.3. Study design: "Case-control" like models is preferred in determining efficacy, whilst a "serial observational parameter changes" model is preferred in determining the safety of the medicinal product being tested.

3.6.2.4. Power of the study and Animal numbers: The number of animals selected for any study has to provide sufficient statistical power (size effect) to ensure that the results obtained from the study are scientifically valid and thus clinically translatable/indicative. It is generally expected that for the study to be valid, the preferred power of study has to achieve 90% (α=0.9).

3.7. "3 R" concept for conducting pre-clinical studies

Although the original principles of 3Rs were first defined in 1959, these have been further expanded today and is appropriately included in the following definitions:

3.7.1. **Replacement:** Testing approaches that avoid or replace the use of live animals in an experiment where they would have otherwise been used. Replacement could include using established animal and human cell lines, cells and tissues, mathematical and computer models, or physicochemical methods.

3.7.2. **Reduction:** Approaches that minimise the number of animals used per experiment or study, either by enabling researchers to obtain comparable levels of information from fewer animals or to obtain more information from the same number of animals, thereby avoiding further animal use. Examples include improved experimental design and statistical analysis, combination of studies, international harmonisation of testing requirements (e.g. VICH) to avoid duplicate testing and the use of technologies, such as imaging, to enable longitudinal studies in the same animals.

3.7.3. **Refinement:** Approaches that minimise the pain, suffering, distress or lasting harm the animals may experience. Refinement applies to all aspects of animal use, from the housing and husbandry used to the scientific procedures performed on them. An example of refinement is the use of appropriate anaesthetics and analgesics.

For the purpose of this document, *In vitro* studies are defined and referenced as studies using part, partial or extracted and/processed materials from animals used in experiments conducted in laboratories for the purpose of research studies as part of marketing/registration authorisation. Whereas *In Vivo* studies (animal studies) are conducted using animals of all types (exclusive of humans and non-primates) to indicate biological responses of a whole organism/animal as a reflection of human biological response for a similar purpose.

3.8. Sources of cells

The extraction, processing, derivation, fragmentation or/and any other related techniques involving the handling of adult cells for the use of preclinical studies are allowed without restriction, provided that these are conducted within the acceptable limits of ethical and legal parameters. Special caution and approval from the local authorities, such as the government institutional research ethics committee, are applied in studies using induced pluripotent stem cells; more so when genetic alteration, mutation or manipulation are employed.

The use of embryonic stem cells is governed under more stringent conditions and must adhere to strict rules drawn and only allowed by NCERT. This guideline is an affirmation of the rules relating to human embryonic stem (hES) cells that are mentioned in the previous guideline (2nd Edition), which states that:

3.8.1. The creation of human embryos by any means, including but not limited to assisted reproductive technology (ART) or somatic cell nuclear transfer (SCNT), specifically for the purpose of scientific research, is prohibited.

3.8.2. To facilitate autonomous choice and avoid conflict of interest, decisions related to producing embryos for infertility treatment should be free of the influence of investigators who propose to derive or use hES cells in research. Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hEC cells should not be the same person.

3.8.3. No cash or in-kind payment may be provided for donating blastocysts in excess of clinical need for research purposes.

3.8.4. Consent for blastocyst donation should be obtained from each donor at the time of donation. Donors who have given a prior indication of their intent to donate for research any excess blastocysts that remain after clinical care should nonetheless give informed consent again when any specific research is being considered. Donors should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.

3.8.5. In the context of donation of gametes or blastocysts for hES cell research, the informed consent process should include the following information:

3.8.5.1. A statement that the blastocyst or gametes will be used to derive hES cells for research may include human transplantation research.

3.8.5.2. A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation.

3.8.5.3. A statement as to whether the identities of the donors will be readily ascertainable to those who derive or work with the resulting hES cell lines.

3.8.5.4. If the donors' identities are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines.

3.8.5.5. An assurance that participants in research projects will follow applicable and appropriate best practices for donation, procurement, culture, and storage of cells and tissues to ensure, in particular, the traceability of the stem cells. (Traceable information, however, must be secured to ensure confidentiality).

3.8.5.6. A statement that derived hES cells and/or cell lines might be kept for many years.

3.8.5.7. A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation.

3.8.5.8. A statement that embryos will be destroyed in the process of deriving hES cells.

3.8.5.9. A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors.

3.8.5.10. A statement of risks involved to the donor.

3.8.6. Research that should not be permitted at this time:

3.8.6.1. Research involving *in vitro* culture of any intact human embryo, regardless of derivation method, for longer than 14 days or until the formation of the primitive streak begins, whichever occurs first.

3.8.6.2. Research in which hES cells are introduced into non-human primate blastocysts or in which any ES cells are introduced into human blastocysts.

3.8.6.3. No animal into which hES cells have been introduced at any stage of development should be allowed to breed.

3.8.6.4. Fusion of human stem cells or other cells of pluripotent nature with cells of non-human origin shall not be permitted to develop beyond 14 days or until the formation of the primitive streak begins, whichever occurs first.

3.9. Demonstration of the scientific validity of modified and new approaches

The amount of information needed and the criteria applied to a new method will depend on a number of factors, including:

3.9.1. The regulatory and scientific rationale for the use of the method;

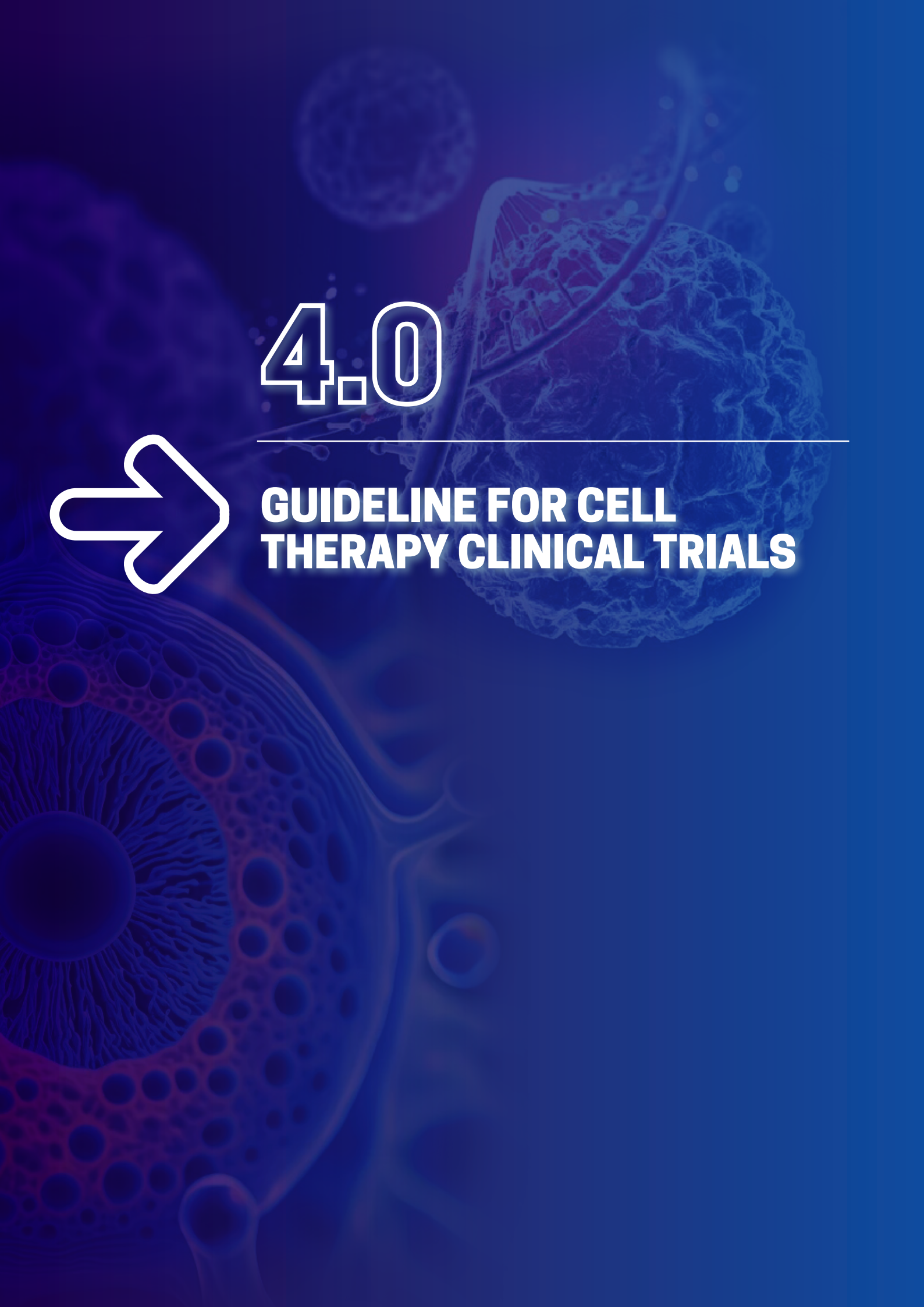
3.9.2. The type of method being evaluated (e.g. existing test, new method);

3.9.3. The proposed uses of the method (e.g. mechanistic, total or partial replacement, as part of a testing strategy);

3.9.4. The mechanistic basis for the test and its relationship to the effect(s) of concern (e.g. whether it is a mechanistic/functional and/or an empirical relationship); and

3.9.5. The history of use of the test method, if any, within the scientific and regulatory communities.

Flexible approaches to demonstrate a method's scientific validity for regulatory use are acceptable, including formal validation by recognised centres for validation. These may include the opinion of an accredited research institute such as public research universities.



4.0

GUIDELINE FOR CELL THERAPY CLINICAL TRIALS

4.0 GUIDELINE FOR CELL THERAPY CLINICAL TRIALS

4.1. Conduct of clinical trials utilising cell and cell-based products

4.1.1. A systematic appraisal that demonstrates evidence to support the intended intervention should be conducted before initiation of clinical trials utilising cell and cell-based product (CCBP). Identification of all potential risks should be acknowledged, identified and minimised throughout all phases of human clinical trials.

4.1.2. Favourable balance of risks and benefits should be an anticipated outcome for clinical trials.

4.1.3. Clinical trials should employ designs that not only minimise risks but also include the smallest number of subjects to properly answer research questions.

4.2. Regulatory pathway and ethical approval

4.2.1. All clinical trials should be prospectively registered in the National Medical Research Register (NMRR).

4.2.2. All clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Malaysian Good Clinical Practice and the applicable regulatory requirement(s).

4.2.3. All clinical trials must obtain prior ethics approval.

4.2.4. For products that require Clinical Trial Import License (**CTIL**) / Clinical Trial Exemption (**CTX**), clinical trials may commence after obtaining both the CTIL/CTX and ethical approval. CTIL/CTX shall only be issued once ethical approval to the relevant ethics or review boards depending on where the clinical trials are to be conducted has been obtained. Valid GMP evidence that contains the following information should be submitted:

1. Name of Investigational Product (IP) manufacturer
2. Address of manufacturing site under inspection
3. Scope of Inspection
4. Dosage form covered during inspection
5. Inspection date
6. Conclusion of the inspection
7. Validity of GMP Status
8. Official Stamp of the Issuing Authority

4.2.5. Cellular therapies that incorporate gene repair or genetic modification must adhere to regulatory guidelines set forth for both cell therapy and gene therapy products. This includes genetic manipulation done ex-vivo, which is administered to the patient.

4.2.6. The Principal Investigator (PI) should determine the product class based on the criteria outlined by National Pharmaceutical Regulatory Agency (NPRA) or by other reputable regulatory bodies such as the US-Food and Drug Administration (US-FDA) and European Medicines Agency (EMA). Products that have had prior regulatory body's approval will follow the class assigned to the product.

4.2.7. Institutional Ethics Committee (IEC) will approve or suggest to PI to revise the product classification.

4.2.8. There are two different pathways for obtaining approval of clinical trials utilising CCBPs. The first pathway is for clinical trials that will utilise Class I and Class II products that have been registered by NPRA (Fig.1a). The second pathway is for clinical trials that will utilize Class II products that do not have prior approval by NPRA (Fig.1b).

For unregistered Class II products, the applicant should apply CTIL/CTX from NPRA.

4.2.9. All research that involves clinical applications of CCBP interventions must be subjected to independent / expert review processes for approval as well as efficacy and safety monitoring.

4.2.10. Additional independent reviewers such as data and safety monitoring boards may be appointed from granting agencies.

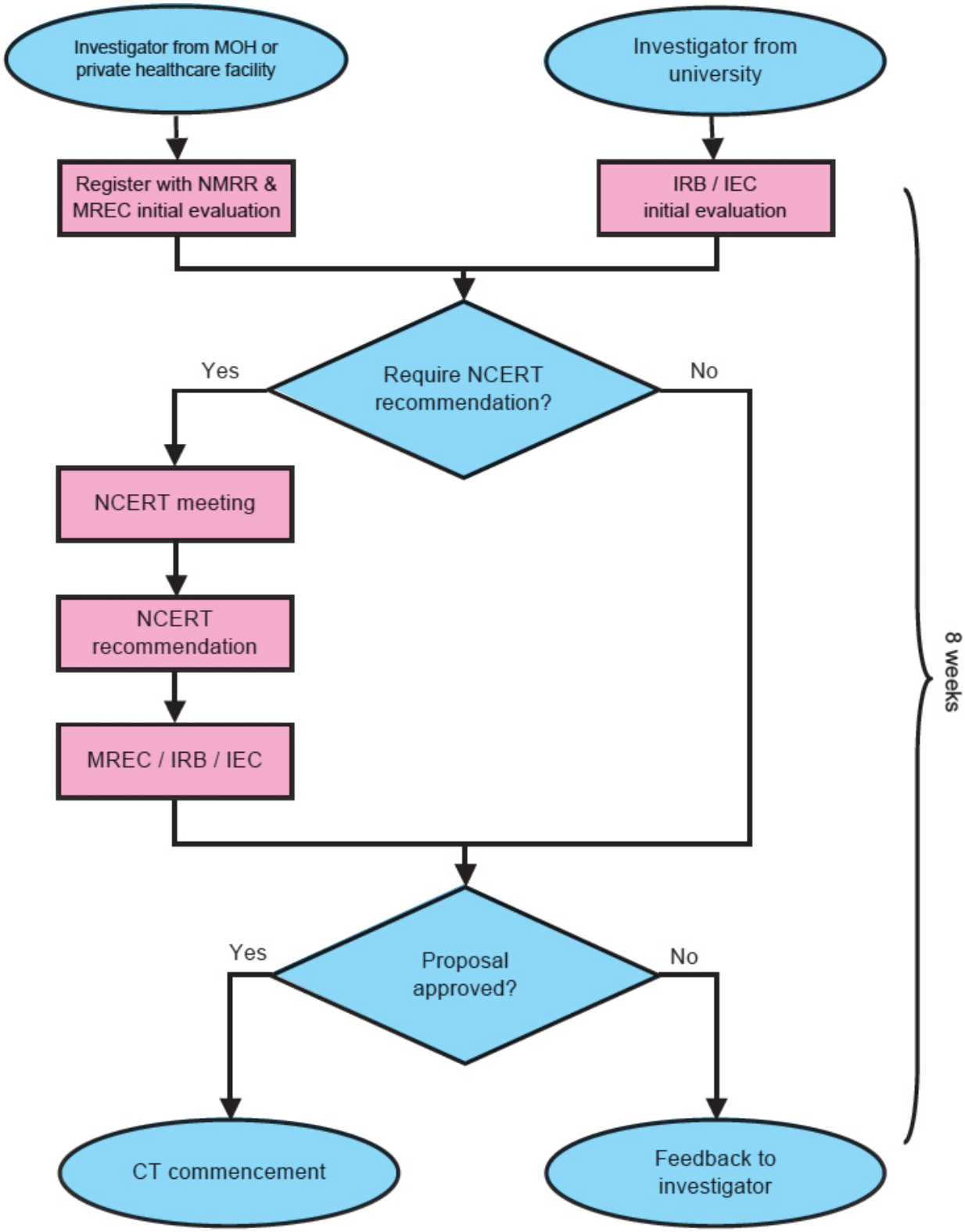


Figure 1a: Clinical trial approval pathway for Class I products and Class II products ***with prior approval from NPRA.***

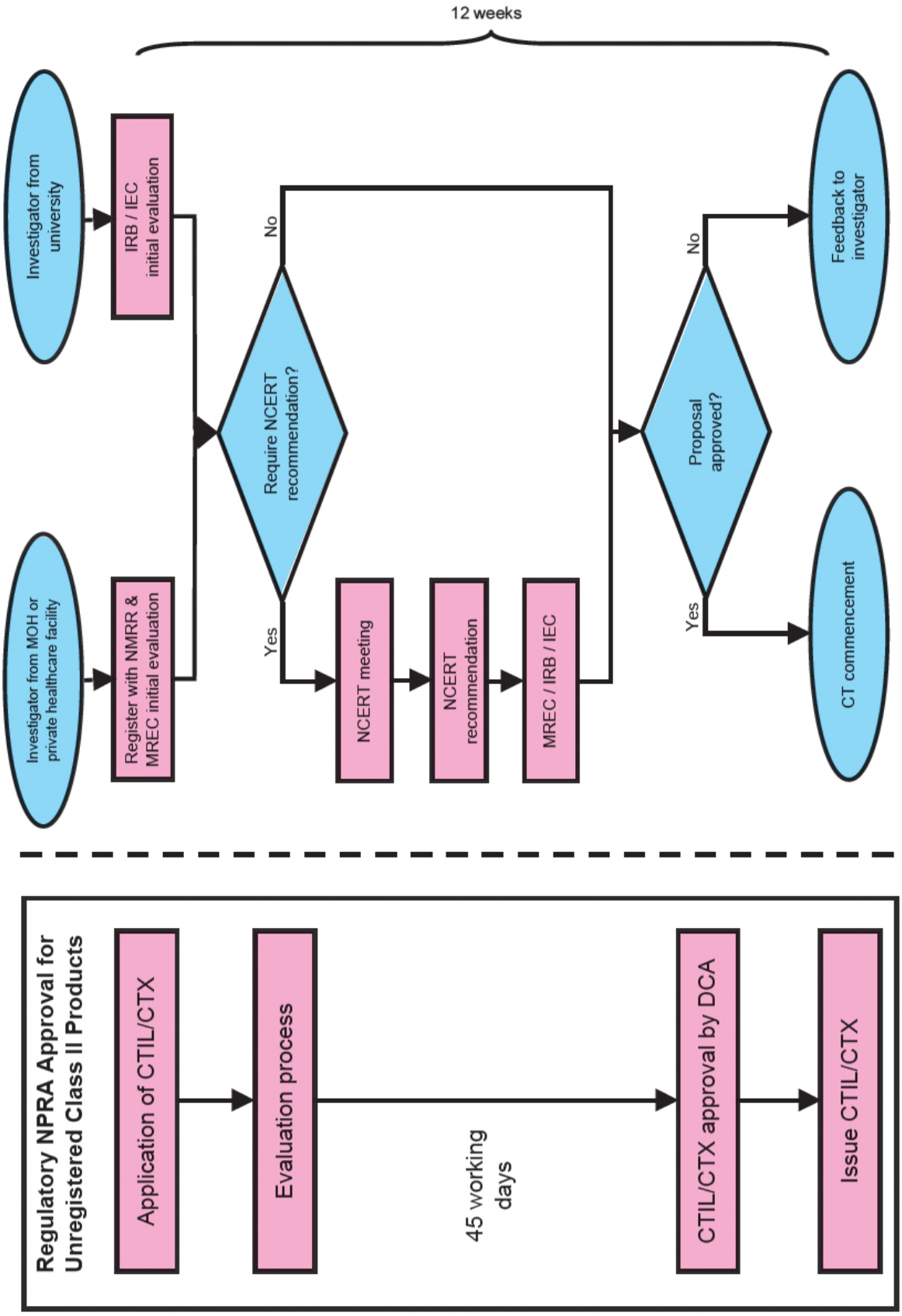


Figure 1b: Clinical trial approval pathway for Class II products ***without prior approval from NPRA.***
Note*: NPRA and clinical trial approval shall be applied concurrently.*

4.3. Investigational product (IP)

4.3.1. Clinical trials (CTs) should, where possible and appropriate, include testing for viability, purity, sterility, genetic stability, proliferation/differentiation potentials, distribution and migration of the cells in the body; and potency/ functionality of the cells.

4.3.2. When planning trials, the sponsor / investigators should ensure that sufficient safety and efficacy data from pre-studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied CTs should compare new interventions against the best therapeutic options that are currently available to the local target population.

4.4. Choice of comparator

4.4.1. Late phase trials should include randomisation and suitable comparator arms.

4.4.2. CTs utilising CCBP should:

4.4.2.1. Compare IP against the best therapeutic approaches that are currently or could be made reasonably available to the local target population; and

4.4.2.2. Should be responsive to the health needs of the country.

4.4.3. Where there is no proven effective treatment for a medical condition and cell-based interventions involve invasive delivery systems, it may be appropriate to test them against placebo or some comparators.

4.5. Clinical Safety and Efficacy

4.5.1. All safety issues arising from the pre-clinical development should be addressed, especially in the absence of an animal model of the treated disease or in the presence of physiologic differences limiting the predictive value of homologous animal models.

4.5.2. Studies on efficacy should:

4.5.2.1. Demonstrate clinically significant efficacy using appropriate clinical endpoints (primary & secondary endpoints)

4.5.2.2. Demonstrate an appropriate dose-schedule

4.5.2.3. Evaluate duration of treatment effect; and

4.5.2.4. Demonstrate benefit-risk assessment compared to existing therapeutic alternatives for the target population.

4.6. Phases in clinical trials utilising cell and cell-based products

4.6.1. Before any treatment modality is approved for use in patients, it has to go through various stages of testing to ensure its correct dose, safety and effectiveness. It is critical to show clear and significant clinical benefit in Phase II studies to ensure that these carry forward to later phase trials (Phase III and IV) where a larger and more heterogeneous patient population whenever is required but not mandatory[2].

Definition of **First-in-Human (FIH) according** to CTIL/CTX guideline as follows:

- First-in-human (FIH) studies start with the initial administration of a novel active ingredient into humans. Traditionally, FIH studies were most associated with a single ascending dose (SAD) design, which was subsequently followed by a multiple ascending dose (MAD) design. FIH studies include clinical trials with a higher dose that has yet to be tested in humans.

4.6.2. Considerations should be given to CCBP for life threatening indications and unmet medical needs conditions to accelerate its availability in the clinics. Novel pathways that allow CCBP conditional marketing approval for use in patients if early phase clinical trials show that the product is safe and likely to predict efficacy. This approach means that CCBP studies may not necessarily follow the usual clinical trial phases if the product is deemed beneficial and lifesaving. Further recommendations should be discussed with the respective regulatory bodies. (Refer Drug Registration Guidance Document (DRGD); Appendix 12: Priority Review and Appendix 13: Designation and registration of orphan drugs by NPRA).

4.7. Subject selection

Subject selection should be done from populations that may benefit from the study, in a fair and non-discriminatory manner. Investigators required to follow subject selection adhering to protocol approved by the ethics committee.

4.8. Informed consent

4.8.1. Participation into CTs should be voluntary and must not interfere with ongoing clinical care. Patients must also be informed that they are free to withdraw from CTs without any penalty.

4.8.2. Efforts must be made to ensure that potential CTs subjects do not overestimate the degree of benefits of the investigational product. Approaches that can be included when obtaining informed consent include using independent party and instating a cooling off period between discussing the CTs and obtaining the consent.

4.8.3. Cell therapies may involve either somatic cell or germline modifications. CCBP therapies are different from usual pharmaceutical or device-based therapy as it may not be removed once administered and its biological effects may be prolonged or have off-target effects.

4.8.4. Providing supplementary materials to potential participants to ensure their full comprehensions of the CTs.

4.8.5. Consent should also include the full process of sample collection, its use, storage and potential uses of left-over samples.

4.8.6. Requirements of post-marketing and life-long monitoring and reporting of adverse event (AE).

4.9. Investigators / Study sites

4.9.1. In addition to fulfilling the criteria set in the current Malaysian Good Clinical Practice (GCP), investigators involved in CT utilising CCBP must be trained in the relevant fields and prove to have the capacity and resources to ensure the studies are conducted with integrity, quality and without detriment to the participants.

4.9.2 Study sites involving private healthcare facilities should comply to the policy and requirements outlined by the Private Medical Practice Control Section (CKAPS), Medical Practice Division, Ministry of Health Malaysia.

4.10. Sponsor / Institution

The sponsor and institution conducting CTs utilising CCBP are responsible to ensure that there is fair inclusion of participants, adequate resources including financial resources for the running of the study and ensuring the safety and well-being of the participants. There must also be processes to ensure the integrity of the data resulting from the CTs. All requirements that involve sponsor / institutional responsibilities and agreements in conducting a CT will follow the current GCP.

4.11. Risk management

4.11.1. There must always be a strategy for ensuring minimal risk throughout the duration of the study period to improve tolerability and increase the efficacy of the treatment.

4.11.2. A risk management plan (RMP) is mandatory for all CTs utilising CCBP and must encompass modification to cell production procedures, cell dose calculation and / or cell administration protocol and any medical procedure involved.

4.11.3. RMPs must include safety reporting and investigating any mortality that occurs during the trial and follow-up period.

4.12. Subject follow-up, monitoring and safety reporting

4.12.1. An independent data-monitoring plan is required for CTs utilising CCBP

4.12.1.1. When deemed appropriate, adverse event (AE) reporting and ongoing statistical analyses should be submitted to an independent peer review or oversight body at predetermined times or on demand.

4.12.1.2. Data monitoring personnel and committees should be independent from the research team.

4.12.2. The risk / benefit balance can change over the course of a study period, as safety and response are observed, recruitment wanes or as new treatments become available.

4.12.2.1. This is especially true for CCBP intervention trials, which are characterised by high uncertainty and rapidly evolving science.

4.12.2.2. The welfare of subjects must be carefully monitored throughout the duration of the study.

4.12.3. The study should be interrupted if the risk / benefit ratio becomes unfavourable.

4.12.4. Subjects should be informed of new information about themselves, the trial or the intervention that might materially affect their willingness to continue participation in a study.

4.12.5. Given the potential for transplanted cellular products to persist and depending on the nature of the experimental CCBP intervention, subjects should be advised to undergo long-term health monitoring:

4.12.5.1. Long-term follow-up provides an opportunity to monitor the emergence of late AE and the durability of benefit.

4.12.5.2. Funding institutions should be encouraged to support long-term follow-up.

4.12.5.3. The duration of the follow-up should be clearly mentioned.

4.13. Autopsy

Autopsy should ideally be performed for subjects who succumb after receiving investigational products and consented to the procedure if the cause of death is uncertain.

4.14. Documentation during Clinical Trials

All CTs utilising CCBP must have documentation that allow for a thorough evaluation of the conduct of the CTs and the quality of the data produced, including demonstration of compliance of the investigator, sponsor and monitor.

4.15. Recording and reporting research results

4.15.1. Pharmacovigilance[2], continued systematic collection and reporting of safety, efficacy and utility data must be continued by the developers, manufacturers, providers and regulators of CCBP after it has entered clinical use that are aligned with institution and regulatory guidelines. Long term follow-up after the end of a clinical trial should be determined based on the nature of the CCBP, its clinical indication and protocol requirement. Results of such monitoring activities should be promptly reported to regulatory authorities and the medical community.

4.15.2. Patient registries should be set up as a method to collect safety and efficacy data of Class II CCBP products. Registry data is an important means of evaluating long term efficacy and cost effectiveness data.

4.16. Appendix 1: Clinical Trials Phases

Phases of CTs.[4]

Study phase	Description
Phase I	a. The first testing done on a small group of people usually 3-5 patients after preclinical testing. The number is justified by the local epidemiological burden of the disease that is being treated. b. Primary objective is to determine safety. c. Requires prior safety and efficacy data from comprehensive preclinical animal studies conducted locally or otherwise. d. The principles of the "3Rs," to reduce, refine, and to replace animal use in testing may be applied if animal study is not feasible. e. Procedures to assess risks of tumorigenicity by an independent body must be established and implemented. f. Procedures on safety monitoring processes must be established by the sponsor/investigator and implemented. This includes setting up an Independent Safety Data Monitoring Committee. g. Procedures to assess side effects and complications are in line with local and international regulations and guidance. h. GCP compliance is required[3] (refer to the 4th edition Malaysian Guideline for Good Clinical Practice, MOH, 2018) and other International Council for Harmonisation (ICH) principles which are applicable in Malaysia.
Phase II	a. Generally performed with the number of subjects double the number of subjects in Phase I, consisting of patients, for further evaluation of safety and efficacy. b. These studies are comparative, determining the difference between the new treatments with either a placebo and/or current available standard treatments. c. Requires data from Phase I trials, which may or may not be performed by the same group of investigators. d. Determines the optimum dose, route, regimen, patient population and endpoints. e. Does not require randomisation in design.

Study phase	Description
	f. Control arm(s) may not be necessary as comparisons can be done against best therapeutic options currently available in the local setting. g. Sponsor / investigator is required to continue with safety data monitoring as in Phase I. h. Established processes are required to assess short-, medium- and long-term effects of investigational CCBP. i. Positive data from Phase II CT can be used to obtain conditional approval marketing provided these trials demonstrate that the tested cell products are safe and "likely to predict efficacy". j. GCP compliance is required.[3]
Phase III	a. Same objectives and methods as Phase II studies except the patient population is much larger, about three times the number of subjects in Phase II (conducted at various geographical sites). b. Requires data from Phase II trials, which may or may not be performed by the same group of investigators. c. Requires randomisation in design. d. Designs that determine safety and efficacy of investigational CCBP. e. Continuation of an Independent Data Safety Monitoring Board. f. GCP compliance is required.[3] **[For uncommon diseases and unmet medical needs situations, a Phase II study is optional and can be replaced by real world data studies or post marketing studies from other countries]**
Phase IV	a. Required to identify and evaluate long-term effects of approved CCBP over a long period of time. This includes specific safety issues such as loss of efficacy, infections, immunogenicity / immunosuppression, malignant transformation and the in-vivo durability of the associated medical device/biomaterial component. b. Requires informed consent. c. Should be described in the risk management plan (RMP) of the CT design. d. Class II CCBP would require development and maintenance of a patient registry.

Appendix 1: The different phases of studies and requirements for CTs utilising CCBPs. Compliance to current GCP is required for all phases.

4.17. Appendix 2: Informed consent specific for collection and use of samples

Items that should be included in the informed consent specific for the collection, storage and use of samples.[14]

Collection process
i. How invasive is the process and what are its additional risks?
ii. How will complications related to the process be treated?
iii. Will there be any consequences in the normal microscopic characteristics of the cells caused by the process?
iv. Protection of privacy if sample collection involves examination of intimate areas e.g. vaginal examination.
v. Will there be monetary compensation in case of injuries or complications during the collection process?
Use of samples
i. Will the samples be used for a specific study (fully restricted use)?
ii. Will the samples be used for the immediate study and in other specific future research that includes a definite time frame (partially restricted use)?
iii. Will the samples be used for the immediate study and in any kind of future research without a definite time frame (unrestricted use)?
iv. Will the samples be used for research involving genetics or genetic modification?
Storage of samples
i. Information on storage of samples for future research and a provision for the subject (or guardian) to decide whether to participate or opt out of future research from stored samples.
ii. Where the samples will be stored and who has access to them and for what?
iii. Duration of storage of the samples.
iv. How the samples be disposed of?
Ownership
i. The research institution will retain ownership of samples.

Appendix 2: Adapted from The World Health Organization (WHO) Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells and Fluid in Research.

5.0

CURRENT LEGISLATION & GUIDELINES OF CELL AND GENE THERAPY PRODUCTS IN MALAYSIA

5.0 CURRENT LEGISLATION & GUIDELINES OF CELL AND GENE THERAPY PRODUCTS IN MALAYSIA

5.1. The cross-boundary nature of cell and gene therapy products (CGTPs) involve a multidisciplinary approach. Therefore, its full control will also be subjected to various other regulations (authorities), hence an integrated oversight is imperative, as follows:

5.1.1. The clinical use / medical procedure of the product will be under the ambit of Medical Development Division, Ministry of Health Malaysia;

5.1.2. The device element of such products must comply with the Medical Device Act and regulations under the ambit of Medical Device Authority (MDA), Ministry of Health Malaysia; and

5.1.3. The National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia (as a secretary of Drug Control Authority) will ensure the medicinal product's quality, efficacy and safety.

5.2. The primary mode of action / the principal mechanism of action by which the claimed effect or purpose of the product is achieved determines whether the product is a drug or a medical device;

5.2.1. Drug is based on pharmacological, immunological or metabolic action.

5.2.2. Medical device does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its intended function by such means. (e.g. mechanical action, physical barrier, replacement of or support to organs or body functions).

If required, applicant may apply for product classification with NPRA.

5.3. The following is the list of relevant legislative documents and guidelines:

5.3.1. Sale of Drugs Act 1952 (Act 368)

5.3.1.1. Control of Drugs and Cosmetic Regulations 1984

5.3.1.2. Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia

5.3.1.3. Malaysian Guidelines for Application of CTIL and CTX

5.3.1.4. Current Drug Registration Guidance Document (DRGD)

5.3.1.5. Current Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products

5.3.2. Private Healthcare Facilities and Services Act 1998 (Act 586)

5.3.3. Biosafety Act 2007 (Act 678)

5.3.4. Medical Device Act 2012 (Act 737)

5.3.5. Human Tissue Act 1974 (Act 130)

5.3.6. Other current relevant guidelines

5.3.6.1. Guidelines for Stem Cell Research and Therapy

5.3.6.2. National Standards for Stem Transplantation

5.3.6.3. National Guidelines for Haemopoietic Stem Cell Therapy

5.3.6.4. National Standards for Cord Blood Banking and Transplantation

5.3.6.5. Surat Pekeliling Ketua Pengarah Kesihatan Malaysia Bil. 04/2015: Tatacara Prosedur Permohonan Berkaitan Penyelidikan Sel Stem dan Cell-based Therapies (Checklist for Research on Stem Cells and cell-based Therapies)

5.3.6.6. General Circular No. 3 Year 1999 Regulation for the Conduct of Research in Malaysia

5.3.6.7. Guidelines on Importation and Exportation of Human Tissue and/or Body parts (CDC 2006)

5.3.6.8. Guidance Note for Cell & Gene Therapy Products (CGTPs) Manufacturing Facility in Malaysia

5.4. Regulatory Framework for CGTPs as a Drug/ Medicinal Product

5.4.1. For CGTPs that are classified as medicinal products, the Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia, which was published in 2016, can be referred. The document is issued by the Director of Pharmaceutical Services under regulation 29 Control of Drugs and Cosmetics Regulation (CDCR).

5.4.2. The following are **included** in the framework:

5.4.2.1. Human stem cells

5.4.2.2. Human tissue therapy products (e.g. skin, cardiovascular, ocular, musculoskeletal tissues)

5.4.2.3. Human cellular therapy products (e.g. cartilage cells, pancreatic islet cells, cultured skin cells, haematopoietic stem/progenitor cells derived from peripheral and cord blood)

5.4.2.4. Genetically modified cellular products.

5.4.2.5. Cell-based cancer vaccines and cell-based immunotherapies

5.4.2.6. Dendritic cells, lymphocyte-based therapies, cell-based therapies for cancer, peptides and proteins.

5.4.3. The following are **not included** in the framework:

5.4.3.1. Fresh viable human organs, or parts of human organs, for direct donor-to-host transplantation.

5.4.3.2. Fresh viable human haematopoietic stem/progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution.

5.4.3.3. Labile (fresh) blood and blood components (e.g. fresh frozen plasma).

5.4.3.4. Unprocessed reproductive tissues (e.g. sperm, eggs, embryos for in vitro fertilization (IVF) and other assisted reproductive technology procedures).

5.4.3.5. Secreted or extracted human products (e.g. milk, collagen).

5.4.3.6. Samples of human cells or tissues that are solely for diagnostic purposes in the same individual.

5.4.3.7. In vitro diagnostic devices.

5.4.3.8. Haemopoietic Stem Cell Therapy (HSCT) products identified as "Established standard of Care (S)" listed in the National Guidelines for Haemopoietic Stem Cell Therapy.

5.4.4. The inclusion and exclusion lists are not self-contained. The lists may be amended as required.

5.4.5. Although the focus of the regulation currently is on human cells and tissues, it is acknowledged that more recently, additional efforts and developments have been directed towards xenotransplantation. Therefore, xenotransplantation has also been included in the framework.

5.5. Risk Classification of Cell Therapy Products (CTPs)

5.5.1. The framework is based on a risk-management system approach, i.e. different levels of regulations are applied to CGTPs based on the risks associated with their use. Thus, two classes/categories of products have been identified. Class I (lower risk cell therapy product) and Class II (higher risk cell therapy products).

5.5.2. For lower risk products, the regulatory framework focuses on minimising the risk of transmission of infectious diseases. A product eligible for regulation as Class I is not subjected to premarket review requirements or approval.

5.5.3. To be a Class I CTP, the product **must meet all four** of the following criteria:

5.5.3.1. It is **minimally manipulated** (not activated, encapsulated, expanded *ex-vivo*, or genetically modified);

5.5.3.2. It is intended for **homologous use*** only as determined by labelling / intended use and advertising;

5.5.3.3. Its manufacture **does not involve combination with another drug / article / device**, except for water, crystalloids, or a sterilising, preserving, or storage agent (not raising new clinical safety concerns for the CTP); and

5.5.3.4. It **does not have a systemic effect** and is not dependent upon the metabolic activity of living cells for its primary function; or **if it has such an effect**, it is intended for **autologous use****.

5.5.4. If a cell therapy product does not meet all the four criteria in Class I, then the product will fall under Class II. A Class II product is "highly processed", used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes". In addition, novel cell and gene therapies products are categorised as Class II. Class II products is regulated as a biologic product. The evaluation for CTIL / CTX approval and product registration requires sufficient data demonstrating that the product is safe and effective in humans. Manufacturer also required to comply with cGMP requirements.

5.5.5. In the clinical development of a Class II product, the quality and scientific evaluation must be adequate to permit an evaluation of the product's effectiveness and safety. Prior to clinical development phase, manufacturing description and pre-clinical pharmacology/toxicology data must sufficiently characterise product quality and safety.

5.5.6. For a combination cell therapy product, proof must also be provided on the drugs and devices used having met the requirements of the relevant legislations. As currently envisioned – most, if not all, stem cell-based therapies will be considered as medicinal product and would be subjected to this framework.

5.5.7. The summary of requirements of cell-based therapies is tabulated below:

Class I	Class II
Compliance to Good Tissue Practice	Regulated by NPRA (registration and licensing) as biologics • Compliance to Good Manufacturing Practice (GMP) • GMP licensing • New product registration framework • Complete control, manufacturing and control • Pre-clinical • Clinical trial • Post-marketing-active surveillance The Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products in Malaysia, published on the NPRA website (www.npra.gov.my), provide guidance on the structure and data requirements for both clinical trial applications and registration applications.

5.6. Good Tissue Practice (GTP)

The quality of the tissues and cells provided from cell and tissue establishments are important to the quality of the final product for human applications. Cells and tissues by their very nature, inherently, pose potential risk to recipients than conventional medicines that may have a sterilisation process included in their manufacture.

Good Tissue Practice (GTP) requirements include requirements for facilities, environmental control, equipment, supplies & reagents, recovery, processing and process controls, labelling controls, storage, receipt and distribution and donor eligibility determinations, donor screening and donor testing.

The aim of GTP is to prevent cell and tissues products with infectious disease agents, and to ensure that these cells and tissues maintain their integrity and function. This guide only focuses on cell and tissue establishments. Reference on detailed methods such as cleanroom classification and monitoring, qualification, validation and quality risk management should be made to other documents such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products Part I and its Annexes. In certain cases, other national regulations or standards may be applicable for cell and tissue establishment whereby it may provide technical requirements for the donation, procurement and testing stages. Cell and tissue establishment shall be responsible to adhere to these requirements (if any) and it must be done in accordance with an appropriate quality system.

Note: This guide should be read in conjunction with the current National Standards for Stem Cell Transplantation, National Guidelines for Haemopoietic Stem Cell Therapy and National Standards for Cord Blood Banking and Transplantation.

5.7. Good Manufacturing Practice (GMP)

5.7.1. Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any production that cannot be eliminated through testing the final product. GMP covers all aspects of production; from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process - every time a product is made.

5.7.2. Therefore, the manufacture of cellular therapy products should be in compliance with the principles of current Good Manufacturing Practices (cGMP). The Pharmaceutical Inspection Convention/Scheme (PIC/S) (www.picscheme.org) cGMP regulations comprise basic requirements applying to all products as well as annexes with detailed requirements for special types of products. Of particular relevance to CGTPs are:

5.7.2.1. Annex 1: Manufacture of Sterile Medicinal Products.

5.7.2.2. Annex 2a: Manufacture of Advanced Therapy Medicinal Products for Human Use.

5.7.2.3. Annex 8: Sampling of Starting and Packaging Materials.

5.7.2.4. Annex 11: Computerised System.

5.7.2.5. Annex 13: Manufacture of Investigational Medicinal Products.

5.7.2.6. Annex 15: Qualification and Validation.

5.7.2.7. Annex 16: Authorised Person and Batch Release.

5.7.2.8. Annex 20: Quality Risk Management.

5.7.2.9. Guide to Good Manufacturing Practice for Medicinal Products (Part II) (Specific Guidance for APIs Manufactured by Cell Culture/Fermentation).

5.8. COMPLAINT AND INQUIRIES

Any complaints and inquiries regarding unregistered CGTPs or unproven therapy can be channelled to the following department:

Drug: Complaints can be lodge either by phone (03-78413200), or through the Civil Service Complaints Management System portal (SisPAA) or through the nearest Pharmacy Enforcement Branch office (https://www.pharmacy.gov.my/v2/en/content/state-pharmaceutical-services-divisions.html).

Device: Medical Device Authority (MDA)
Any complaints and inquiries can be lodged through the MDA Feedback Management System (FEMES) (https://femes.mda.gov.my/).

Practice: Malaysian Medical Council (MMC)

Facilities and Services: Private Medical Practice Control Section (CKAPS), Medical Practice Division, MOH
Any complaints and inquiries can be lodged through https://myckaps.spab.gov.my/eApps/system/index.do

6.0

CHECKLIST FOR RESEARCH ON STEM CELL AND CELL-BASED THERAPIES

6.0 CHECKLIST FOR RESEARCH ON STEM CELL AND CELL-BASED THERAPIES

NMRR ID:	
Study Protocol Title:	
Principal Investigator:	

NOTE: **Study Principal Investigator (PI):**
Please indicate whether the ITEMS outlined are present in the study protocol or any other documents; if present, state the page number of each item. Once completed, please submit the completed form to MREC/IRB/IEC to be checked and forwarded to NCERT.

ITEMS	To be completed by Study PI			To be completed by MREC/ IRB/IEC
	State (Y) for 'Yes', (N) for 'No', (NR) if not relevant	Document name and page number	Other Remarks (if any)	State (Y) for 'Yes', (N) for 'No', (NR) if not relevant
1. Pre-clinical studies (investigators must show their own data and not from other laboratories)				
1.1 Approval letter from animal ethics committee is recommended				
1.2 Testing in animal research facility which is GLP compliance				
1.3 Evidence that the pre-clinical studies was subjected to rigorous and independent peer review and regulatory oversight				
1.4 Safety data in small animals				
1.5 Safety data in large animals				

1.6	Comprehensive toxicology data in small animals (including contamination, acute infusional toxicity, deleterious immune responses, unexpected behaviour of the cellular product, and tumorigenesis)				
1.7	Comprehensive toxicology data in large animals (including risks of contamination, acute infusional toxicity, deleterious immune responses, unexpected behaviour of the cellular product, and tumorigenesis)				
1.8	Proof of principle of the desired effect (that the cells have repaired the damage/ disease) – unequivocal efficacy data				
1.9	Show biological distribution data				
1.10	Show evidence of physiologic integration and long-lived tissue reconstitution				
1.11	Show that differentiation (either in vitro before transplantation or in vivo after transplantation) occur only along the desired lineages				
1.12	Design based on clinical expectations				
1.13	Mechanistic studies to show biology (done by the group)				
1.14	GLP compliant for testing				
1.15	Evidence that the pre-clinical data has been submitted to the NPRA				
2.	**Phase I trials**				
2.1	For first in human studies conducted locally, to provide accreditation of Phase I FIH facility(ies)				
2.2	Comprehensive pre-clinical studies have been done and data showed safety and efficacy in animals (performed by the group) is recommended				

2.3	Procedures on how the cells be tracked in terms of homing to the target area, viability and longevity of the cells				
2.4	Procedures on how the safety be monitored				
2.5	Procedures to assess risks of tumorigenicity by an independent body must be implemented				
2.6	Procedures to assess short-, medium- and long-term side effects				
2.7	GCP compliance for investigators				
3.	**Phase II trials**				
3.1	Data from Phase I trials (performed by the group themselves and if the trial is not performed by the group, explain why the data should be used for this trial)				
3.2	Procedures on how the cells be tracked in terms of homing to the target area and viability of the cells				
3.3	Optimisation of dose, route, regimen, patient population, endpoints, and controlled				
3.4	Procedures on how the safety be monitored				
3.5	Independent data safety monitoring board				
3.6	Plan to assess short-, medium- and long-term side effects				
3.7	GCP compliance for investigators				
4.	**Phase II trials**				
4.1	Data from Phase II trials (performed by the group themselves)				
4.2	Conduct 'randomised' control				
4.3	Design to show safety and efficacy				
4.4	Independent data safety monitoring board				
4.5	GCP compliance for investigators				

5.	**Cell processing and manufacturing**				
5.1	Evidence by a letter of conformance for GMP compliance and issued by relevant authority				
5.2	Show evidence of relevant processes: Standard operating procedures, quality standards, environmental control, equipment qualification, analytical methods, audits, staff training, etc.				
5.3	Cell processing and manufacture of any product must be conducted under scrupulous, expert, and independent review				
5.4	Demonstrate that the product is safe, pure and potent				
6.	**Product registration**				
6.1	Show that the product has been registered with the National Pharmaceutical Regulatory Agency before use in human trials				
6.2	License for clinical trial has been obtained (CTIL/CTX)				
7.	**Cell characterization (pre-requisite to clinical trials)**				
7.1	History of the cells in the stem cell or cell-based product				
7.2	Biological characterisation of cell type				
7.3	Demonstration of purity				
7.4	Demonstration of potency (e.g., cells produce insulin in a physiological manner)				
7.5	Manufacturing standards and independent certification, where relevant				
7.6	Evidence that cells are free from contamination				

7.7	Evidence of viability and longevity of cells after transplantation (to determine the likely duration of the therapeutic effect)				
7.8	Evidence that cells will home into the area of damage or repair				
7.9	Evidence of genomic stability during culture				
8.	**Investigators and researchers**				
8.1	Is the Principal Investigator trained in cell transplantation? (Show evidence of credentialing)				
8.2	Are other investigators trained in cell transplantation? (Show evidence of credentialing)				
8.3	Qualifications of scientists and researchers				
8.4	Registration with National Medical Research Register, Ministry of Health				
9.	**Centres performing therapy (Information for patients)**				
9.1	Registration with PHCFS Act, Ministry of Health				
9.2	Informing subjects about the human embryonic cell source, if applicable				
9.3	The unique risks and disclose honestly that the treatment have not been tried before				
9.4	Utmost clarity on the potential benefit				
9.5	Disclosing financial and non-financial conflicts of interest				
9.6	Provide monitoring patients long term				
9.7	Providing a clear, timely, and effective plan for adverse event reporting				

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