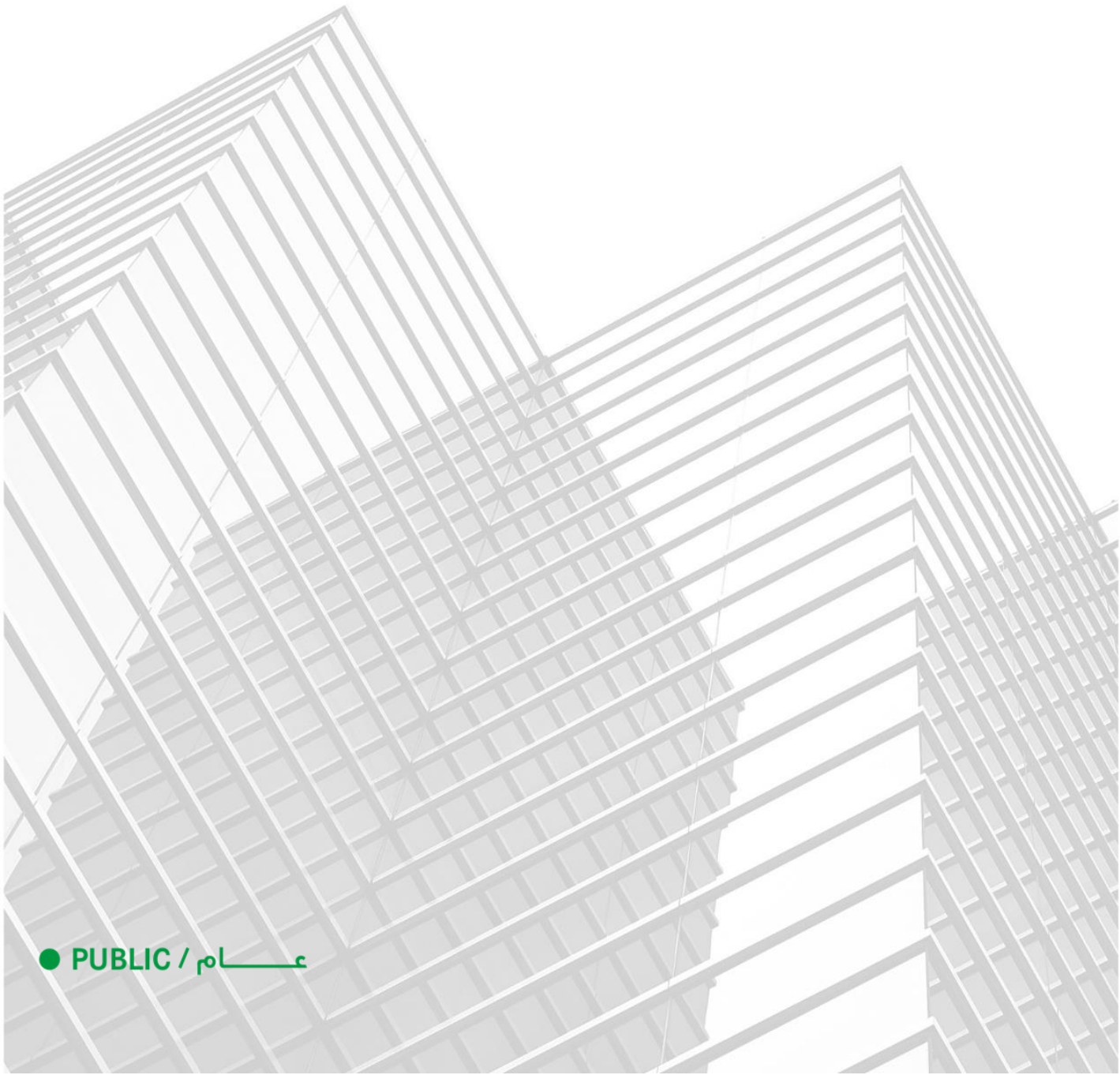
دائـــرة الـصـحـة
DEPARTMENT OF HEALTH

Guidelines for Clinical & Translational Research in Stem Cells



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1.Guideline Purpose and Brief

Although the process of clinical translation of potential stem cell-related treatments is not a recent phenomenon, this guideline addresses certain aspects that have not been effectively addressed and may contribute to the optimization of new interventions. In addition, ethical issues related to stem cell manipulation and processing are addressed, as well as the need for collaborative agreements between private and public sector organizations for an integrated perspective between research, public health, academic institutes, and commerce.

This guideline provides recommendations for conducting safe, effective and sustainable stem cell research and its translation into clinical practice by maintaining compliance with policies and legal norms of Abu Dhabi and international ethical principles. It does not describe all the requirements and processes; it is recommended to review related policies and standards published.

The guideline can be used by all DOH-licensed healthcare providers, authorized health payers, oversight committees, suppliers of stem cells products and laboratories performing activities related to stem cells, stem-cell based-products and related cellular therapies for the purpose of human use, health insurance products and schemes, healthcare and medical facilities, academic institutes conducting human subjects research and/or clinical translational research, and stakeholders with interests in health-related products and services.

These recommendations do not apply to research conducted with non-human stem cells or derivatives that are not intended for human use. Moreover, it will complement the established medical care standards treatments based on hematopoietic stem cells.

2. Definitions and Abbreviations

No.	Term / Abbreviation	Definition
2.1	**ADHRTC**	**A**bu **D**habi **H**ealth **R**esearch and **T**echnology **C**ommittee is an oversight committee that has been established by DOH to oversee and support critical human subject research carried out by various healthcare providers from public or private healthcare providers, and to advise on and promote health research in the Emirate of Abu Dhabi.
2.2	**Advanced Therapy Medicinal therapy**	Special categorization of drugs, that include gene and cell therapy drugs as well as tissue engineering drugs.
2.3	**Allogeneic Stem Cell**	Stem cell derived from different individuals than the donor, that will be used for medical or research purposes, such as tissue repair or potential cure.
2.4	**Autologous stem cell**	Stem cell derived from the same individual that will be used for medical or research purposes, such as tissue repair or cell-based therapies. It carries the same DNA and human leukocyte antigen (HLA) from the human subject.
2.5	**Basic research**	Earliest stage of research, usually developed in a laboratory with *in-silico*, organoid, *in-vitro*, or *in-vivo* models. It is conducted for the advancement of knowledge, often without any emphasis for its potential practical applications.
2.6	**Biobank**	Large collection of human biological materials (biospecimens) held for health and medical research purposes. Biobanks contain relevant personal and health information (which may include health records, family history, lifestyle, and genetic information).
2.7	**Biological materials**	Products used to diagnose, prevent, treat, and cure diseases and medical conditions. These products maybe produced through biotechnology in a living system and are often more difficult to characterize than small molecule drugs. These include therapeutic proteins, monoclonal, antibodies, vaccines, among others.
2.8	**Chimera**	Organism that contains cells from two or more genetically distinct individuals. It can occur naturally or be created artificially through genetic engineering techniques.

2.9	**Clinical Translational Research**	Research that focuses on translating basic scientific discoveries from the laboratory and taking them into clinical practice to improve individual and population health outcomes.
2.10	**Clinical Trial**	Research study performed in humans that aims to evaluate a medical, surgical, or behavioral intervention.
2.11	**Compassionate use**	Treatment option that allows the use of an unauthorized medicine alone or in combination with other available therapeutics. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials.
2.12	**Drug**	Chemical substance intended to modify the structure or any function of the human body or other animals. They are commonly used for the diagnosis, cure, mitigation, treatment or prevention of disease.
2.13	**General Data Protection Regulation (GDPR)**	European Union Law (and the European Economic Area, EEA) that that regulates privacy and security of human data since 2016.
2.14	**Good Laboratory Practice (GLP)**	Set of rules and criteria for a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are performed.
2.15	**Good Manufacturing Practice (GMP)**	Set of rules that guarantees that production processes are performed according to quality requirements.
2.16	**Good Tissue Practice (GTP)**	Set of quality standards and guidelines that govern the collection, processing, storage, and distribution of human tissues for medical use. GTP ensures that tissues are safe, effective, and traceable, and that they meet regulatory requirements.
2.17	**Healthcare facility/facilities**	Entity licensed by the Department of Health of Abu Dhabi that is involved in the direct delivery of healthcare and/or supportive healthcare services, or in the financing of health such as health insurer and health insurance facilitator, healthcare claims management entity, payer, Third Party Administrator (TPA's), hospital, medical clinic and medical center, telemedicine provider, laboratory and diagnostic center, and pharmacy, among others.
2.18	**Homologous use**	Therapeutic use of cells or tissues within their native physiological context, for example, the transplantation of hematopoietic stem cells to regenerate blood cells or the use of adipose tissue to reconstruct a breast.
2.19	**Human biological material**	Cell, tissue and/or fluid derived from a human organism, such as saliva, blood, umbilical cord, placental tissue, among others.
2.20	**Human Embryonic Stem Cell (hESC)**	Pluripotent cell capable of differentiating into all somatic cell types of a human being. It is found in the inner cell mass of the human blastocyst during days 4 to 7 after fertilization.
2.21	**Human embryo**	Multicellular structure that can give rise to all the tissues and organs of the human body, it represents the earliest developmental stage starting from fertilization until the first eight weeks of
2.22	**Incidental finding**	Observations, results, or other findings that may occur during analysis but are unrelated to the primary goals of the analysis.
2.23	**Research Ethics Committee (REC)**	Independent body formally designated to review, approve, and monitor biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the subjects. Also called Institutional Review Board (IRB) in some countries

2.24	**Induced pluripotent stem cell (iPSCs)**	Differentiated cells that have been reprogrammed to a pluripotent state, meaning they can differentiate into any cell type in the body. They are created by introducing specific genes into the adult cells, essentially "turning back the clock" to a more embryonic-like state.
2.25	**Institutional Stem Cell Research Committee (ISCRC)**	Specialized and multidisciplinary oversight body established within the facility to review all aspects of stem cell research and applications performed.
2.26	**Minimal manipulation**	Processing level of cells and tissues that does not alter the original relevant characteristics and structure related to their original function or their relevant biological characteristics. For example: isolation, separation, washing, culturing without biological and chemical treatment, among others.
2.27	**Mitochondrial Replacement Techniques (MRT)**	Novel procedures designed to prevent the maternal transmission of mitochondrial DNA (mtDNA) diseases, which are rare, severely debilitating, progressive, and often fatal in infancy or childhood.
2.28	**Non-homologous use**	Intended therapeutic use of cells outside their native physiological context, for example, the transplantation of hematopoietic cells or mesenchymal stromal cells into the heart or brain.
2.29	**Off-label use**	Use of approved pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.
2.30	**Organoid**	Three-dimensional structure that is grown *in vitro* and mimics the architecture and function of an organ. It is typically derived from stem cells or tissue cultures.
2.31	**Oversight process**	Systematic mechanism that monitors and supervises research activities to ensure compliance with ethics, policies, regulations, and quality standards.
2.32	**Persistence**	Refers to the characteristic of stem cells to self-renew and maintain their undifferentiated state over time.
2.33	**Pluripotent**	Cell capable of differentiating into every typology of human organism cells, but not able to induce a new organism.
2.34	**Preclinical research**	Stage of research before clinical trials, where feasibility, iterative testing, and drug safety data are collected, typically in laboratories with animal models.
2.35	**Regenerative medicine**	Branch of medicine that focuses on the development of new therapies to repair, replace or regenerate damaged or diseased cells, tissues or organs and involves the use of stem cells, tissue engineering and other advanced technologies to promote healing and to restore normal function.
2.36	**Somatic Cell**	Any cell type of an organism but the reproductive cells.
2.37	**Stem Cell**	Undifferentiated and unspecialized cell that has the capacity to regenerate (self-renewal) through cell division for long periods of time and which, under certain physiological or experimental conditions, can be induced to differentiate into specialized cell types (differentiation) with specific morphological characteristics and functions.
2.38	**Stem cell-based embryo models**	Three-dimensional structures that simulate the early stages of embryonic development using stem cells. They are used to investigate the mechanisms of embryonic development, model diseases and test drugs.
2.39	**Substantial manipulation**	Processing level of the biological material that alters the main original characteristics and functions. The processes include isolation, purification, genetic manipulation, tissue culture, amongst others.

I. SECTION 1: GENERAL CONSIDERATIONS

1. PRINCIPLES

1.1. To achieve an effective research and clinical translation that promotes confidence between all parties involved. Healthcare facilities should conduct stem cell research (basic, preclinical, and clinical) by achieving the following principles (**Figure 1**).

1.1.1. **Essentiality: Active** human participation in the research is considered essential after the evaluation of up-to-date alternatives and knowledge.

1.1.2. **Voluntariness:** participation depends on informed consent where all aspects of the research are briefed, including the risks and benefits for the participant and the wider community. The possibility of withdrawal of participation is offered and transparent.

1.1.3. **Non-exploitation:** Physical, psychological, and moral implications related to the research are addressed irrespective of the socioeconomic status and educational level of the participants.

1.1.4. **Privacy and confidentiality:** a participant's identity is protected, unless valid scientific and legal reasons are provided for disclosure.

1.1.5. **Risk minimization:** Appropriate and well-informed risk-benefit analysis must be performed whereby the overall wellbeing of research subjects must not be voided.

1.1.6. **Professional competence:** Conduction of the research depends on competent and qualified personnel with integrity and impartiality.

1.1.7. **Maximization of public interest and distributive justice:** The benefits must be distributed, focusing on unmet public health needs. The costs of the investigational product should not represent a barrier to its access and use.

1.1.8. **Transparency and accountability:** the research must be conducted in a fair, honest, unbiased, and transparent manner, by disclosing the interests of the parties involved and declaration of any possible conflict of interests.

1.1.9. **Institutional arrangements:** Subsequent uses and applications of the research should be transparently executed. The institution should ensure that research reports are accurately documented and the materials used and data generated are preserved and archived with auditable traceability.

1.1.10. **Public domain:** Research results should be published, maintaining the privacy of participants, and remain available to researchers and those associated without unnecessary delay.

Figure 1: Principles for effective research and clinical translation.

1.2. Research on human participants involving cells and tissues derived from human sources must safeguard human rights, safety, dignity, and fundamental freedom.

1.3. Ethical boundaries should be respected during all phases of the research.

1.4. Evidence and knowledge generated from stem cell research should be trustworthy to make accurate healthcare decisions by healthcare professionals and payers.

1.5. Regulation of the use of stem cells should be clearly defined to encourage and promote investors participation in the development of products and therapies related to stem cells.

2. SPECIFIC ISSUES FOR STEM CELLS RESEARCH

2.1. **Procurement of stem cells**

For the isolation of stem cells from human biological materials, a voluntary informed consent must be obtained from the donors before the research commences (whether it is basic, preclinical, or clinical).

2.1.1. The informed consent document should comply with DOH Standard on Human Subject Research, DOH Standard on Protective Health Information, and DOH Guidelines for Research and Clinical Translation in Genomics (if applicable).

2.1.2. The consent process should be robust and include the following information, in a manner that donors can comprehend it:

2.1.2.1. Need for screening of transmittable diseases they may not be aware of, such as: HIV (NAT testing), hepatitis B virus, hepatitis C virus (NAT testing), *Treponema pallidum*, human T-lymphotropic virus (HTLV-1), cytomegalovirus, amongst others.

2.1.2.2. Need for screening of any other risk factors, including possible genetic disorders and cancer.

2.1.2.3. Policies and procedures for the return of results should be developed on the consent process by the research healthcare facility, including measures for dealing with incidental findings and the donor's preferences about retrieval of information.

2.1.2.4. Risks involved during the collection of cells and/or tissues.

2.1.2.5. Possible use of the donated biological material for the generation of cell lines and products, that may be banked and/or shared with other scientists.

2.1.2.6. Potential commercialization applications of the genetically modified materials or derivatives, where the intellectual property rights will not vest with the donor. If this commercialization brings financial benefits, efforts to pass on the same to the donor and community should be made, if possible.

2.1.2.7. Established mechanism of re-contacting donorsfor future requirements

2.2. **Manufacture of stem cells and its derivatives**

Manipulation of stem cells is necessary to produce cell lines, products, and therapies. These manipulations include isolation, enrichment, *in vitro* expansion, induction of pluripotency, differentiation, amongst others. For these purposes, the following is recommended:

2.2.1. Stem cell-based products and services for human use should be only processed under Good Manufacturing Practices (GMP) and Good Tissue Practices (GTP) in DOH licensed facilities.

2.2.2. Measures to ensure that stem cell derived products are safe for human application should be adequately addressed. Some of the factors that may comprise risk to stem cell therapy recipient are:

2.2.2.1. Differentiation potential of the stem cells

2.2.2.2. Source (autologous, allogeneic)

2.2.2.3. Type of genetic manipulation, if applicable.

2.2.2.4. Homologous and non-homologous use (if applicable)

2.2.2.5. Persistence in the recipients: how long do stem cells last within the recipients.

2.2.2.6. Differentiation into tissues or organs.

2.2.2.7. Potential abnormal growth of transplanted cells.

2.2.2.8. Contamination with infectious agents.

2.2.2.9. Reagents, cells, and supplements that may induce immune reactivity.

2.2.2.10. Reagents, cells, and supplements originated from animals that may introduce xenogeneic pathogens.

2.2.3. Special considerations should be taken with pluripotent stem cells, since they hold the risk of acquiring mutations after prolonged maintenance in culture, to grow and differentiate into inappropriate cellular phenotypes, to form benign teratomas or malignant outgrowths, and to fail in maturation processes.

2.2.4. Animal models and surrogate analysis can be used for testing the potency and viability of cryopreserved or stored stem cells.

2.2.5. Standard Operative Procedures (SOPs) should be put in place for the entire process from the obtention of the biological specimen to intermediate products and ultimately to the final product. It is recommended that these documents are as detailed as possible and reviewed regularly.

2.2.5.1. Information of cultivation passages and genetic evaluations should be declared in the SOPs.

2.2.5.2. Inclusion of flow diagrams in SOPs are recommended to increase understanding.

2.3. **Review and oversight mechanisms**

Research related to stem cells is associated with unique ethical, legal, and social concerns that require additional oversight and expertise for efficient scientific and ethical evaluation.

2.3.1. A specialized oversight process that monitors and evaluates the unique scientific, legal, and ethical aspects associated with stem cells research should be established.

2.3.2. The oversight process should be performed at the institutional and at the national level by separate mechanisms.

2.3.2.1. The review must be carried out by the Abu Dhabi Health Research and Technology Committee (ADHRTC) at the national level to monitor compliance with policies, legislation, and ethical norms of Abu Dhabi. It is suggested that ADHRTC promotes the position of these therapies in Abu Dhabi for patients with poor therapeutic response if scientific rationale is met.

2.3.2.2. An Institutional Stem Cell Research Committee (ISCRC) Or the local Research Ethics Committee (REC) should be established to conduct the oversight process at the institutional level, that complies with the characteristics and responsibilities described in DOH Standard on Human Subject Research and that maintains expertise related to the stem cell research (basic and clinical).

2.3.2.3. If the above is not possible, institutional oversight can be performed by an Independent Ethics Committee (REC) at the local, regional, or international level if the process occurs effectively, impartially, and rigorously.

2.3.3. The conformed ISCRC/REC must be approved by DOH to perform the oversight process.

2.3.4. The ISCRC/REC should be capable of assessing the scientific merit and rationale, expertise of the researchers, and ethical justification related to stem cell research.

2.3.5. The ISCRC/REC/IRB must be composed of a minimum of 9 members who are not directly engaged in the research. These should include:

2.3.5.1. Qualified scientists and/or physicians, with relevant expertise in stem cell biology, assisted reproduction, developmental biology, and clinical medicine.

2.3.5.2. Ethicist(s) familiar with implications and justifications related to the sensitive elements of the stem cell research under consideration.

2.3.5.3. Legal and regulatory experts with relevant knowledge on local policies and statues related to the research.

2.3.5.4. Community members who remain impartial and analyze the benefits of the stem cells research for the participants, patients, and the community, considering their needs.

2.3.5.5. Additional professionals with expertise in the related topics of the research, such as: human genetics, molecular biology, biotechnology, bioinformatics, amongst others.

2.3.6. ISCRC should not be considered as the Institutional . Both approvals of ISCRC and REC should be obtained to guarantee ethical and quality practices related to human stem cell research.

2.3.7. The oversight bodies, both institutional and national, should:

2.3.7.1. Be able to advise researchers in the categorization of the research (See 3.1)

2.3.7.2. Determine if a research proposal is considered as permissible or non-permissible research.

2.3.7.3. Monitor and periodically review ongoing research.

2.3.7.4. Oversee the provenance of the stem cell lines.

2.3.7.5. Introduce improvements in monitoring of the research.

2.3.7.6. Manage and streamline the administrative management of biomedical research, while maintaining the human participant's rights.

2.4. **Applications**

2.4.1. The clinical use of stem cells and derivatives, besides approved indications for hematopoietic stem cell transplantation, should not be commercialized or marketed as therapies since they are still under evaluation in clinical trials. The application of unproven stem cell-, cell-, and tissue-based therapies should be referred to as "stem cell-, cell-, or tissue-based interventions".

2.4.2. Premature commercialization of unproven interventions should be avoided, since it can:

2.4.2.1. Jeopardize patient's safety.

2.4.2.2. Promote futher unauthorized stem cell research.

2.4.2.3. Reduce the willingness to participate in clinical trials.

2.4.2.4. Create and/or promote confusion regarding the scientific, ethical, and clinical state of stem cell research.

2.4.3. No administration of stem cell-, cell-, and tissue-based interventions to humans should be allowed unless it is regulated under the purview of clinical trials or medical innovations (e.g.: compassionate use or expanded access pathways,

2.4.3.1. These clinical trials should follow DOH Guidelines for Conducting Clinical Trial with Investigational Products and Medical Devices (MOHAP). Approvals from ADHRTC, ISCRC/REC/IRB prior to the intervention are required.

2.4.3.2. Interventions under medical innovations terms related to stem cells and derivatives should only be provided after approvals of ISCRC/REC. A plan of action that covers the scientific rationale, ethical and legal justifications, and items described in **Table 1** should be provided for evaluation.

Table 1. Recommendations for medical innovations related to stem cells and derivatives.

Medical innovation	Recommendations
Off-label use	- Uncertainties associated to the off-label use of a drug/therapy should be identified, addressed, and informed to the patients (e.g.: long-term safety and effectiveness). - Off-label use should be supported by high quality evidence. - The plan of action should be compliant with current scientific knowledge, national legislation and/or international standards of medical associations. - Physicians should conduct supervised studies to assess the safety and efficacy of the interventions. These results can help regulatory bodies to expand the scope of a product labelling.
Compassionate use	- Pre-approval non-trial access to experimental stem cell-, cell-, and tissue-based interventions must be approved by ADHRTC in addition to the institutional oversight mechanisms. - Uncertainties associated to the compassionate use of the investigational product should be identified, addressed, and informed to the patients (e.g.: potential side effects, effectiveness, safety). - Compassionate use of the investigational medical product should not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication. - A controlled program should be developed, where the potential benefits justify the potential risks associated to the treatment.

2.4.4. A robust and understandable informed consent should be developed for treatment purposes. The potential recipients must sign the voluntary informed consent prior to the intervention.

3. REGULATION AND RELATED DOCUMENTS

The following documentation can be used to support stem cell research and its clinical translation in Abu Dhabi, but are not limited to:

3.1. DOH Standard on Human Subject Research.

3.2. DOH Standard on Patient Healthcare Data Privacy

3.3. DOH Guidelines for Patient Consent.

3.4. DOH Guidelines for Conducting Clinical Trial with Investigational Products and Medical Devices (MOHAP).
3.5. DOH Standard for Healthcare Facility Licensure.
3.6. DOH Standard for Assisted Reproductive Technology Services and Treatment.
3.7. DOH Standard for Center of Excellence in Hematopoietic Stem Cell Transplantation (HSCT) Services for Adults and Pediatrics.
3.8. Council of Ministers' Decision No. (6) of Near 2020 on Endorsement of the Regulations of Cord Blood and Stem Cells Storage Centers

Recently published stem cell related regulatory tools on local, federal, and international level will support stem cell research.

II. SECTION 2: LABORATORY-BASED STEM CELL RESEARCH

Laboratory-based research (basic research) with stem cells is necessary to enhance knowledge and understanding of diseases, the underlying pathophysiology, developmental biology, potential therapeutic uses, toxicity screening, and the functioning and properties of stem cells themselves. For all of these, stem-cell based embryo models, pluripotency induction techniques, *in vitro* cell culture systems and others are required to be performed under rigorous oversight, consistent with international statements of ethical and scientific principles and with policies and laws of Abu Dhabi.

This type of research does not intend to have clinical practices; however, the outcomes and evidence generated can support healthcare providers to make clinical decisions. Therefore, basic research should follow quality control during all its processes.

1. RESEARCH CATEGORIES

1.1. Research projects can be exempt from review, subject to review, or not allowed depending on the materials used and the processes therein. To uniformize these classification criteria among healthcare facilities, it is recommended to use the ISCCR Guidelines for Stem Cell Research and Clinical Translation for research categorization. (Summary shown in **Figure 3**)
1.2. The investigators should declare the project-related information to the ISCRC/REC, and ADHRTC (if applicable) for evaluation prior to the beginning of the laboratory practices. It is recommended to refer to Form#05 USE OF STEM CELL, ZYGOTES, GAMETES AND FETUSES IN RESEARCH of DOH Standard on Human Subject Research.
1.3. The ISCRC should determine under which category the research relies on after the evaluation of protocols and provided information.
1.4. Human biological materials derived from licensed biobanks do not need ISCRC/REC nor ADHRTC approval for *in vitro* protocols.

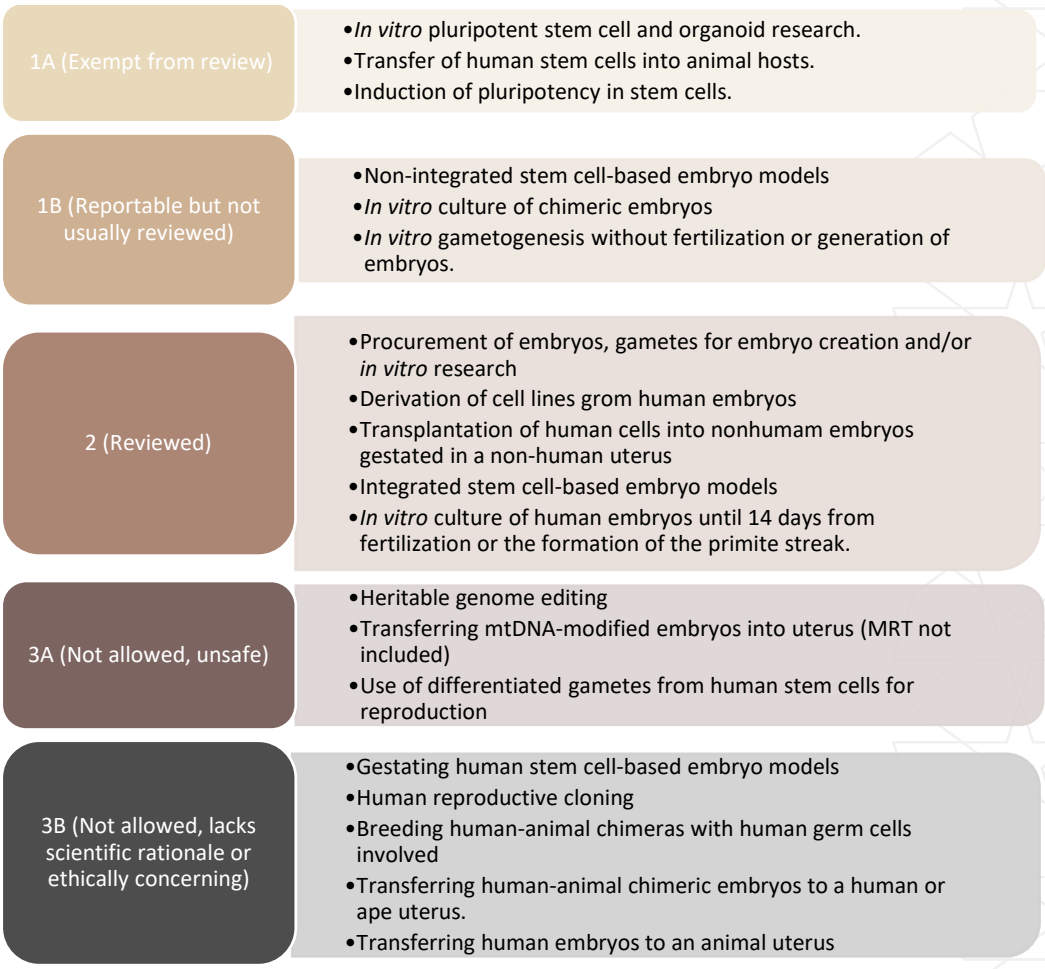

Figure 3. Research categories for review. Adapted from ISCCR Guidelines for Stem Cell Research and Clinical Translation

2. HUMAN BIOLOGICAL MATERIALS

The obtention of human biological materials for basic research purposes should comply with the indications mentioned in 2.1 for voluntary informed consent, excluding the documents related to clinical trials.

2.1. **Consent**

2.1.1. To leverage the benefits of donated materials and protect the donor's privacy, the informed consent process should be clearly articulated.

2.1.2. It is recommended that the person who conducts the informed consent dialogue does not have a vested interest in the research protocol to avoid conflicts of interest and bias.

2.1.3. Space and time to answer questions to the donors should be provided.

2.1.4. Counselling services to donors should be provided.

2.1.5. If secondary researchers use the biological materials, the policies and statements of the primary research should be respected.

2.1.6. Measures to maintain privacy and confidentiality of donors must be considered for the access and sharing of materials and information, since it holds genomic information and the potential to connect de-identified samples to the donors and its relatives. It is recommended to follow DOH Guidelines for Research and Clinical Translation in Genomics and the European Union Law on General Data Protection Regulation (GDPR).

2.1.7. Dynamic, flexible, and broad consents are recommended to allow a vast range of applications for the donated materials. Nevertheless:

2.1.7.1. The use of donated materials for reproductive purposes requires an additional specific consent.

2.1.7.2. The informed consent for research purposes is not the same for clinical treatment.

2.1.8. Procedures for the obtention of the human biological material should seek to minimize the risks associated.

2.1.9. Clinicians and clinics where informed consents for fetal tissue is sought should not profit from the research financial outcomes.

2.2. **Source and intended use**

The ISCRC/REC should review the human biological material procurement based on its source and its intended use, as it is shown in **Figure 4**. Additional recommendations are provided in *Specific Issues off Stem Cells Research* of this guideline.

2.2.1. Procurement of cell lines from biobanks or biorepositories is permissible if their deposition, distribution, and if the secondary uses comply with the statements of the original consent.

2.2.1.1. Certification, ethical approvals, and the original consent should be mandatory for the deposition of human biological materials into biobanks.

2.2.1.2. Cell lines from biobanks should not be used for reproductive purposes under any circumstance.

2.2.1.3. Besides biobanks, cell lines and materials derived from vendors require consistency with the original donor consent.

2.2.2. Procurement of fresh cells and tissues for embryo and stem cell research require ISCRC/REC and ADHRTC approvals prior to the collection process.

2.2.2.1. To maximize the comprehension of the informed consents, international standards for stem cells research informed consent can be used, such as the template documents provided by the ISSCR guideline.

2.2.2.2. The informed consent should include key aspects of human stem cell research if the original human biological materials will be modified to obtain induced pluripotent stem cells.

2.2.3. For gametes and embryos use in research, efforts to prevent undue inducements and exploitation of donor populations, related to any compromised ability to offer voluntary consent, should be requested and evaluated by the ISCRC/REC.

2.2.3.1. For gamete-donated made embryos, consent should be obtained from all the parties involved.

2.2.3.2. For fetal tissue donation, consent from all parties involved should be considered. It the previous is not possible, consent from the female is sufficient.

2.2.4. The use of stem cells derived from any of the previous sources mentioned for research purposes should comply with Abu Dhabi laws and DOH regulations.

Figure 4. Review process guides based on human biological material source and its intended use.

2.3. **Payments and compensations**

2.3.1. The ISCRC/REC should evaluate all reimbursement proposals for out-of-pocket expenses of donors of embryos, sperm, and somatic cells.

2.3.2. If previously stored materials are later used in research, no reimbursement should be retrieved for storage costs prior to the donor's consent.

2.3.3. No reimbursement must be offered for the provision of embryos and fetal tissue, with exemption of out-of-pocket expenses.

2.3.4. For the provision of oocytes:

2.3.4.1. It is recommended to compensate women donating oocytes outside of clinical treatments due to the nonfinancial burdens related to the procurement of the gametes; however, this compensation should not constitute an undue inducement and should be free of exploitation.

2.3.4.2. No payments nor rewards should be given for the quality or number of oocytes provided for research.

2.3.4.3. The procurement must be performed only by qualified physicians (licensed and must have expertise in the specialty).

2.3.4.4. Clinics or third parties involved in the consent obtention, or collection of tissues should not be paid for the provision of tissues for research purposes.

3. HUMAN STEM CELL LINES: BANKING, DERIVATION, AND DISTRIBUTION

3.1. **Derivation of human stem cell lines:**

3.1.1. Proposals for derivation of new Human Embryonic Stem Cell (hESC) should be reviewed by the ISCRC/REC and ADHRTC, if applicable (depending in intended use and source of origin). The approval should require:

3.1.1.1. Scientific justification and scope of the study

3.1.1.2. Qualified personnel with appropriate expertise in Good Tissue Practice (GTP) and Good Laboratory Practice (GLP).

3.1.1.3. Procedures and SOPs for banking the new hESC line.

3.1.1.4. Transparent efforts to distribute the new hESC line to the research community after its publication, if feasible.

3.1.1.5. Documented plans for characterization, storage, and distribution of the cell line.

3.1.1.6. Safeguard measures to protect the privacy of donors.

3.1.2. Policies for encouraging the deposition of cell lines into centralized repositories should be developed in every healthcare facility conducting stem cell research.

3.2. **Deposition of human stem cell lines**

3.2.1. Depositors should provide all available technical information related to the derivation of the cell lines and make it available for researchers. For example:

3.2.1.1. Methods and SOPs used for derivation.

3.2.1.2. Culture conditions.

3.2.1.3. Passage numbers.

3.2.1.4. Disease testing.

3.2.1.5. Cell line characterization and quality controls (e.g.: phenotype, homogeneity, stability, uses, genome editing methods if applicable).

3.3. **Access and distribution**

3.3.1. Material transfer agreements (MTA) between institutions / companies must be developed, including limitations, restrictions, and obligations set by the donor regarding its donated human biological material.

3.3.2. Biobanks should retain MTAs while safeguarding the materials for a minimum of 15 years.

3.3.3. Research financed by public funds should encourage the accessibility of the materials to the research community, if scientifically and ethically appropriate purposes are met.

3.4. Distribution of cell lines with autologous applications should not be available for general distribution until approved.

4. MANIPULATION AND PROCESSING

4.1. Stem cells and cell lines established for basic research shall not be used for human application or clinical trials. Investigators intending to use stem cells or cell lines for clinical trials need to process and develop these cells and cell lines in a DOH certified GLP, GTP and GMP facility.

4.2. No *in vitro* studies on pre-implantation human embryos shall be carried out beyond 14 days of fertilization or formation of primitive streak, whichever is earlier.

4.3. No *in vitro* manipulated cells shall be implanted in human/animal uterus with the intent of developing a whole organism.

4.4. hESCs and iPSCs and/or lines established by the investigator should be registered with ADHRTC through ISCRC.

4.5. Research related to human germ line gene therapy and reproductive cloning is not allowed under the current state of scientific knowledge and understanding.

5. BIOSAFETY

Laboratory biosafety and biosecurity activities are fundamental to protecting the laboratory workforce and the wider community against unintentional exposures or releases of potential pathogenic biological agents.

5.1.1. Laboratory procedures must follow biosafety measures during all processes.

5.1.2. It is recommended to implement a biosafety programme that follows indications of international guidelines, such as:

5.1.2.1. NIH Biosafety in Microbiological and Biomedical Laboratories 6th edition.

5.1.2.2. WHO Laboratory Biosafety Manual. 4th edition.

5.1.2.3. WHO Biosafety Programme Management.

5.1.3. Biosafety measures should beimplemneted according to a risk assessment.

5.1.4. Infection control measures when manipulating human biological materials and the derived stem cells should be developed.

5.1.5. Donated materials should be tested for transmittable diseases. All materials should be considered as potentially infectious during its manipulation.

III. SECTION 3: CLINICAL TRANSLATION OF STEM CELL PRODUCTS AND THERAPIES

Stem cell and genomic editing research holds significant promise for regenerative medicine and cell- and gene-based therapies. Therefore, new interventions must undergo well-designed clinical trials approved by regulatory authorities before being offered to patients. Premature clinical trials can compromise the future development of the technology. Stem cell science profits from following robust guidance to develop evidence-based therapies.

1. CLASSIFICATION OF STEM CELL RELATED INTERVENTIONS

Stem cells and derivatives require a variable degree of *in vitro* or *ex vivo* processing before their use in clinical applications and clinical translational research, which carries the risk of contamination and may also lead to alteration in their properties, which may vary according to the degree and type of manipulation. Based on these, the following classification is provided for stem cell-, cell-, and tissue-based interventions and the considerations needed for their regulation and approved use.

1.1. **Minimally manipulated stem cell-, cell-, and tissue-based interventions:**

1.1.1. Include stem cells, cells, and tissues that have homologous use (e.g.: tissues that are transferred from one part of the body to another, such as adipose tissue).

1.1.2. Moreover, these have undergone simple steps of isolation/separation, washing, centrifugation and suspension in a culture medium/reagent, trituration, moulding and overnight culture without biological or chemical intervention and decellularization.

1.1.3. The categorization of stem cell-, cell-, and tissue-based interventions as "minimally manipulated" excludes them from certain regulatory oversight. Therefore, the responsibility for adequate classification lies with the clinician, who must be able to justify and discern the nature of the classification according to the intervention to be performed.

1.1.4. The healthcare provider has the potential to execute the clinical application of minimally manipulated interventions for homologous use without ADHRTC approval, but ISCRC/REC monitoring is required.

1.2. **Substantially manipulated stem cell-, cell-, and tissue-based interventions:**

1.2.1. Therapies based on stem cells, cells and tissues that have been substantially modified in their structural or biological characteristics due to processes, such as isolation, purification, tissue culture, cell expansion and genetic manipulation, amongst others, must be proven safe and effective prior to their incorporation into clinical care and/or commercialization.

1.2.2. Safety and efficacy should be strictly tested at preclinical and clinical studies as drugs, biologics, and advanced medicinal therapies.

1.2.3. The safety and efficacy will be assessed by the intervention and the disease to be addressed. Therefore, it is imperative to contemplate only the implementation of those interventions that have already been investigated, to protect patients from potential risks.

1.2.4. The clinical applications of substantially manipulated interventions require approval from ISCRC/REC and ADHRTC.

1.3. **Non-homologous use of stem cell-, cell- , and tissue-based interventions:**

1.3.1. Therapies based on stem cells, cells and tissues that are for non-homologous use must be proven safe and effective prior to their incorporation into clinical care and/or commercialization.

1.3.2. Safety and efficacy should be strictly tested in preclinical and clinical studies as drugs, biologics, and advanced medicinal therapies.

1.3.3. The clinical application of all non-homologous interventions requires the approval of ISCRC/REC and ADHRTC.

1.3.4. The benefit-risk ratio for this type of interventions should be assessed, which will depend on the intervention and the specific use.

1.3.5. Well-designed and carefully controlled preclinical and clinical studies are necessary to evaluate the safety and effectiveness of non-homologous interventions.

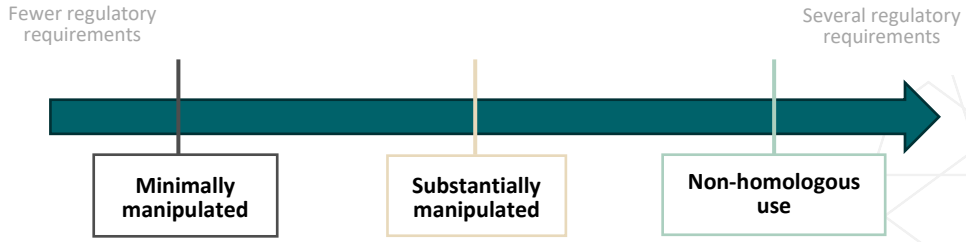

Figure 5. Regulatory requirements for the use of stem cells, cells, and tissues in medical interventions.

1.4. When there is uncertainty or disagreement about the regulatory status of interventions, it is best to contact the Abu Dhabi Health Research and Technology Committee (ADHRTC) and/or an international specialized body (e.g.: The Embryonic Stem Cell Research Oversight of the Institute of Medicine and National Research Council, the Stem Cell Research Oversight committee of the Human Fertilization and Embryology Authority of UK.) and seek their guidance on how specific interventions are classified.

1.5. It is also recommended to adhere to international standards for the classification of cell-based interventions, such as The US Food and Drug Administration (FDA), European Medicines Agency (EMA), Australian Therapeutic Goods Administration, Japanese Ministry of Health, amongst others.

2. PRECLINICAL STUDIES

Preclinical studies serve the critical purpose of assessing the safety and efficacy of a new therapy or drug prior to initiating clinical trials in human subjects. These investigations are typically conducted in animal models and *in vitro* systems, and are designed to identify potential safety concerns, establish appropriate dosing regimens, and evaluate treatment efficacy under highly controlled laboratory conditions.

To commence clinical trials that involve stem cell-based interventions in humans, it is imperative for healthcare facilities to possess convincing evidence of safety and potential clinical utility. Such evidence is obtained through rigorously designed preclinical studies in suitable *in vitro* and/or animal models. Regulatory oversight and independent review are essential prerequisites before initiating clinical trials.

2.1. **Initial considerations**

2.1.1. Preclinical studies should be preceded by a rigorous demonstration of safety, biodistribution and efficacy in early phase human studies.

2.1.2. For animal welfare and ethical considerations, preclinical research should integrate the principle of the four Rs:

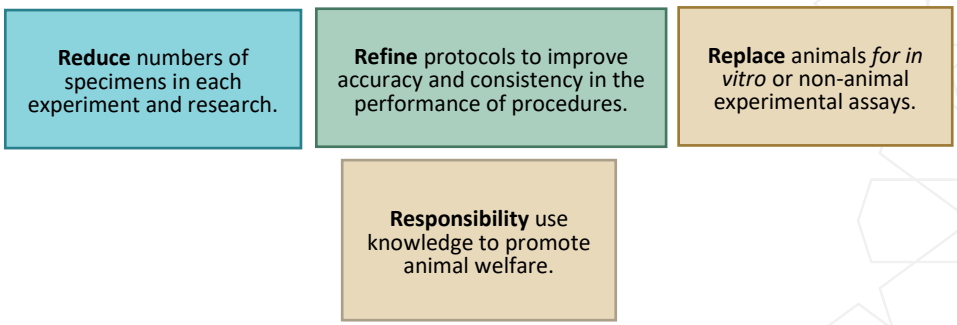

Figure 6. Principles of three "Rs" for animal welfare

2.1.3. To develop new preclinical studies, the healthcare facility should:

2.1.3.1. Be licensed by DOH.

2.1.3.2. Submit the project to the ADHRTC for approval.

2.1.3.3. Have a Research Ethical Committee (REC) with a section for animal ethics principles.

2.1.3.4. Have an Institutional Stem Cell Research Committee.

2.1.4. According to the use of animal models, the healthcare facility should consider the ethical principles for the use of small animals in research and/or be authorized for the use of large animals or non-human primates by obtaining prior approval from an ethics committee related to animal research.

2.1.5. Similar to clinical trials, preclinical experiments rely on research models to mitigate biases in the research (**Figure 7**). Additionally, it is crucial to minimize the impact of confounding variables by controlling them as much as possible during the design phase.

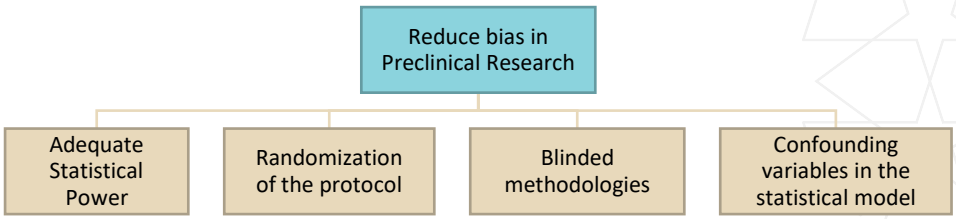

Figure 7. How to reduce bias in preclinical research

2.1.6. To ensure the success and reliability of a clinical trial, it is essential that both investigators and sponsors ensure that preclinical study models are relevant to the clinical trial setting and that they match the human disease and phenotype at the outset. It is also necessary that the outcome measures are optimally matched to the clinical results and demonstrate the mechanism of the treatment effect.

2.1.7. If the results discovered are found efficacious in preclinical stem cell trials have results, it is necessary to replicate in animal models. The investigator will be able to define whether it is necessary to do so in parallel.

2.2. **Pre-clinical Safety Studies**

To demonstrate the safety of a product in a preclinical stem cell trial, investigators must be certain of:

2.2.1. **The type of stem cells:** the type of the stem cells used must be clearly defined and there must be sufficient scientific evidence and justification to support their use. In addition, they must have been assessed for early and late toxicities, including immunogenicity and tumorigenicity.

2.2.2. **Toxicity assessment**: A thorough assessment of the tumorigenicity risks of the product is necessary, especially if cells are manipulated in culture or genetic modifications are carried out, or if pluripotent stem cells are used. This assessment should be performed prior to initiating clinical trials. It is important to perform a genotoxicity and toxicity assessment for product development, depending on the intended clinical use. In addition, an immunogenicity assessment should be included in the repeated dose toxicity study.

2.2.3. **Selection of the animal model**: it is essential to choose a suitable animal model that allows the safety and efficacy of the treatment to be evaluated, and that is as relevant as possible to the disease under study.

2.2.4. **Dose and administration:** the dose and mode of administration of the stem cells should be carefully evaluated to avoid adverse effects and ensure maximum efficacy of the treatment. Toxicity investigations in relevant animals should be carried out using single and repeated dose administration. The form of administration should be similar to that intended for use in the clinical setting.

2.2.4.1. The selection of dosage levels should include information on the dose-response relationship, including identification of the toxic dose and the no-observed adverse effect level (NOAEL).

Repeated dose toxicity studies are only necessary if the intended clinical use involves administration of multiple doses.

2.2.4.2. The interaction between stem cells and drugs, including those with immunosuppressive properties, needs to be tested in relevant animal models, where relevant, for the treatment of the underlying disease.

2.2.5. **Study time:** the study period could extend beyond the established protocol for single-dose chemical toxicity assessment. This is because the cells or biological substances administered may generate long-lasting effects in the body.

2.3. **Pre-clinical Efficacy Studies**

Before conducting preclinical efficacy studies with stem cells, it is important to consider the following:

2.3.1. **Stem cell selection:** The selection of a stem cell that is both safe and effective in its use is imperative. Additionally, investigators should consider whether the stem cell is autologous or allogeneic.

2.3.2. **Animal models:** The animal models used in the trial must be appropriate for the pathology being treated and must comply with ethical and legal standards. Additionally, they should be chosen to evaluate the efficacy of the stem cells.

2.3.3. **Trial design**: The trial must be well-designed and controlled to ensure accurate and reliable results. An adequate number of animals should be determined to detect significant effects and to retain accordance to the four Rs for animal welfare (**Figure 6**).

2.3.4. **Stem cell administration:** The administration of stem cells must be carefully controlled, including dose, route of administration, and frequency.

2.3.5. **Outcome assessment**: Clear criteria must be established to assess the efficacy of the treatment. This may include evaluating clinical, histopathological, and biochemical parameters.

2.3.6. **Long-term follow-up:** Long-term follow-up is essential to assess the long-term safety and efficacy of stem cells.

2.3.7. **Regulatory considerations**: Compliance with applicable rules and regulations for conducting preclinical stem cell trials, particularly those related to ethics and animal welfare, is of paramount importance.

2.4. **Bio-distribution Studies**

When performing stem cell biodistribution studies, it is important to consider the following factors:

2.4.1. **Study design:** The study design should be well planned and include adequate control groups, sample sizes and appropriate time points for the analysis.

2.4.2. **Method of administration**: The route of administration of stem cells should be carefully paced, as it may affect the distribution of the cells throughout the body.

2.4.3. **Labelling of the cells**: it may be appropriate to label the stem cells with a suitable marker to allow tracking and analysis of their distribution. The labelling technique used should not affect the viability or function of the cells.

2.4.4. **Method of detection**: The method used to detect and quantify stem cells should be sensitive and specific.

2.4.5. **Sample collection:** Tissue and fluid samples collected for analysis should be representative of the target areas of interest, and collection methods should not affect stem cell viability or distribution.

2.4.6. **Data analysis:** Data collected should be carefully analysed using appropriate statistical methods to determine the distribution of stem cells throughout the body.

2.4.7. **Safety:** The safety of stem cell therapy should be evaluated in parallel with the biodistribution study, as the distribution of stem cells throughout the body may have implications for their safety and efficacy.

3. CLINICAL RESEARCH WITH STEM CELLS

As mentioned above, cell therapies are an ever-evolving branch of regenerative medicine, allowing a wide variety of diseases to be treated using specialized cells. Clinical trials are crucial for evaluating the safety and efficacy of these therapies in real patients, and there has been a significant increase in the number of clinical trials in this area in recent years. The following recommendations need to be followed by all interested healthcare facilities in conducting clinical trials with stem cell-related products and treatments in Abu Dhabi:

3.1. **General considerations**

3.1.1. Healthcare facilities should ensure the safeguarding of human rights and dignity since DOH has established that human clinical trials must be conducted in adherence to the Declaration of Helsinki.

3.1.2. Any clinical trial should have strong and effective internal policies for the protection of the rights and health of participants, and that these policies are designed to override any interests of science, the state, or the public.

3.1.3. All interventional clinical trials in Abu Dhabi require approval by the ADHRTC, according to DOH Guidelines for Conducting Clinical Trials with Investigational Product and Medical Devices.

3.1.4. Compliance with Section 1 General Considerations, Principles, Specific Issues on Stem Cell Research and Regulation should be met to perform Clinical Trials with stem-cell based products in Abu Dhabi.

3.1.5. Clinical trials should be justified to require the participation of human subjects in terms of risk-benefit assessment which is derived from published literature and previous preclinical studies.

3.1.6. Stem cell-, cell-, and tissue-based products for clinical trials should be processed only under Good Manufacturing Practices (GMP) and Good Tissue Practices (GTP).

3.1.7. The procurement (collection, biobank access, or importation) of the human biological materials, stem cell and cell lines for use in clinical trials should comply with related published DOH Standards in this field.

3.1.8. Detailed management of adverse events must be established in compliance with DOH Standard for Adverse Events Management & Reporting.

3.1.9. Modifying the nuclear genome of human embryos for the purpose of reproduction is premature and should not be permitted.

3.2. **Oversight and review process**

3.2.1. The oversight process performed should be prospective and with ongoing monitoring by an Independent Ethics Committee.

3.2.2. Recommendations given in Specific Issues on Stem Cell Research applicable to clinical trials should be followed.

3.2.3. The review process for stem cell-based clinical research should ensure that protocols are vetted and regularly reviewed by independent experts to evaluate:

3.2.3.1. The *in vitro* and *in vivo* preclinical studies that form the basis for proceeding to a trial, and

3.2.3.2. The design of the trial, including the adequacy of the planned endpoints of analysis, statistical considerations, and disease-specific issues related to human subjects' protection.

3.2.4. REC and ADHRTC should determine if the clinical trial would lead to important knowledge and/or improvement in health.

3.3. **Reagents**

3.3.1. All reagents utilized for the derivation, expansion, and processing of cell lines should be of clinical grade (pharmacopoeia grade).

3.3.2. If research grade materials are used, a quality control program should be included to test safety, purity, and potency of the materials.

3.3.3. Animal derived materials and reagents should be tested for adventitious agents.

3.3.4. The use of serum free and xeno-free cell mediums is encouraged. If not possible, these reagents should be certified and purchased from reputable commercial brands and/or their use should have been proven safe and beneficial in cell-based interventions.

3.3.5. Limits should be established for the concentration of components, including those of animal origin, in the final product.

3.4. **Consent**

3.4.1. Informed consents should include information about:

3.4.1.1. Current status on the application of stem cells in the given condition, the experimental nature of the proposed clinical study and its possible short and long-term risks and benefits.

3.4.1.2. Irreversibility of the intervention

3.4.1.3. Source and characteristics of stem cells and the degree of their *ex vivo* manipulation, if any.

3.4.1.4. The established standard of care for a given condition.

3.4.1.5. The sample size, duration of study and follow-up.

3.4.1.6. The ISCRC/REC, and ADHRTC approvals.

3.4.1.7. Trial characteristics (e.g.: blinded/randomized/open labelled, among others)

3.4.1.8. ~~And how to ask questions, and who to contact~~ **Informed consent for further Inquiries must include a 24 hour contact in that institution**

3.4.2. It is recommended to obtain separate informed consent when a biological sample from treated patients is required.

3.4.3. The possibility of performing a partial or complete autopsy in the event of death of the research participant could be considered in the informed consent, to maximize scientific advances and knowledge on cellular implantation and functional consequences.

3.5. **Trial participants**

3.5.1. Recruitment of participants should be conducted in a population that will benefit from the research outcomes.

3.5.2. There should be no exclusion of individuals for participation in stem-cell based clinical trials unless rational scientific justification.

3.5.3. Efforts to maintain an equal gender distribution of research participants must be made.

3.5.4. The selection of participants for the trials should comply with the predefined inclusion and exclusion criteria of the approved protocol.

3.5.5. Human participants enrolled for clinical trials are not liable to pay any charges towards procedures, investigations and/or resulting hospitalization related to the trial.

3.5.6. A long-term follow-up plan should be implemented considering the nature of the stem cell-based intervention and the persistence potential of cellular products. This plan should be evaluated by ISCRC/REC.

3.5.7. Stem cell participants in clinical trials require a 15-year mandatory annual reporting about genotoxicity and tumorigenesis to the DOH

3.6. **Transparency**

3.6.1. The publishing of results (whether positive, negative, or inconclusive) should be done without unnecessary delay, according to international reporting guidelines, including registration in public databases**.**

3.6.1.1. As an example, researchers could report all randomized trials according to the statement recommendations by the Consolidated Standards of Reporting Trials (CONSORT)

3.7. **Mitochondrial Replacement Techniques (MRT)**

3.7.1. The use of these interventions should only be considered with patients at high risk of transmitting serious mitochondrial-based diseases to their offspring, and when there is no other treatment available.

3.7.2. Long-term follow up should be feasible to apply MRT and requires a 15-year mandatory

3.7.3. annual reporting about genotoxicity and tumorigenesis to the DOH

3.7.4. Sharing of information is recommended to update the knowledge in the field.

4. NEW MEDICAL INNOVATIONS

Although in recent years there has been significant progress in the field of regenerative medicine and other interventions related to stem cell-based technologies, these cells could differentiate into different specialized cell types and therefore offer great potential for treating various diseases and injuries.

It is extremely important to consider that the safety and efficacy of most stem cell-based interventions are undetermined, and premature commercialization puts patients at risk and causes confusion about the actual state of scientific and clinical development. Therefore, it is essential to consider:

4.1. As the processes for stem cell treatments are complex, they should not be developed outside a formal clinical trial that follows national regulations. Exemptions can be considered for unmet medical needs, by following off-label use and compassionate use regulated programs.

4.2. Cell processing and manufacture of any product should be conducted with scrupulous, expert, and independent review and oversight to ensure the integrity, function, and safety of cells for use in patients.

4.3. Manufacturing cells introduces an additional risk of contamination with pathogens and the potential for accumulating mutations and genomic and epigenetic instabilities.

4.4. General recommendations involve considerations for cell processing and manufacture to ensure the safety and efficacy of stem cell-based therapies. For that reason, operating procedures for cell processing, intervention and future commercial application in emerging therapies and drugs should be standardized.

4.5. New clinical trials can be generated when discovering new uses for a stem cell-related treatment or drug, as each clinical trial will demonstrate its safety and efficacy for every potential use.

4.6. Orphan medicine in development to treat rare diseases using cell or gene therapies involving stem cells may be a promising alternative for patients with rare diseases and no effective treatment options. It is important to note that the development of orphan drugs related to stem cell innovation is still in the early stages, and more research is needed to determine the safety and efficacy of these treatments.

5. EDUCATION AND TRAINING OF STAKEHOLDERS

Stakeholder education and understanding in the stem cell field is particularly relevant because of the complexity and controversy surrounding this developing area of biomedical research. Stakeholders, which include researchers, patients, regulators, companies, patient advocacy groups and society at large, must be informed and educated about the various types of stem cells, their potential therapeutic applications, as well as the risks and limitations of these therapies. In addition, ethical and safety issues in stem cell research and use must be addressed. Increased awareness and education can help build public confidence and improve the acceptance of these therapies in the future. To ensure the above, the stakeholders should:

5.1. **Promote STEM education in schools**: STEM (Science, Technology, Engineering, and Mathematics) education is crucial in preparing the next generation of stem cell researchers. Educational programs involving students in stem cell research and experimentation should be implemented.

5.2. **Develop online educational resources**: Online educational resources such as videos and teaching materials can be an effective tool in stem cell education and training. These resources should be accessible and available in different languages to reach a wider audience.

5.3. **Offer training courses and workshops**: Training courses and workshops are an excellent way to educate professionals and inspire students interested in stem cells. Courses should include information on stem cell biology, genomics, therapeutic applications, and research techniques.

5.4. **Establish strategic partnerships**: Global strategic partnerships between academia, industry, and healthcare professionals can help strengthen education and training in stem cells, as well as sharing resources and pooling knowledge. These partnerships can promote collaborative research, standardize professional training, and the faster development of new therapies.

5.5. **Foster scientific outreach**: Scientific outreach can help educate the public about stem cells and their therapeutic applications and benefits. Scientists and healthcare professionals can participate in public conferences and seminars to discuss stem cells and disseminate their research in a clear and accessible language for the public.

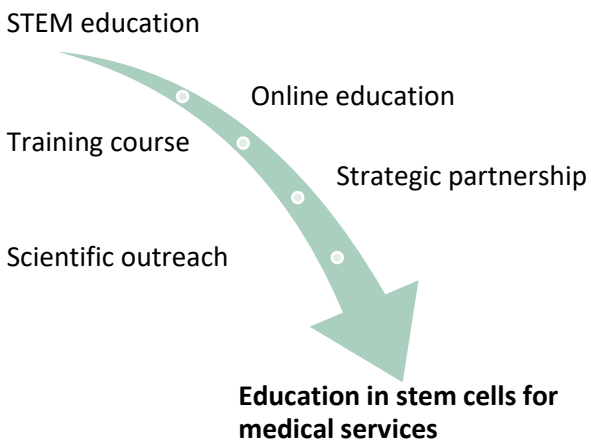

Figure 8. Stakeholders' education in stem cells

IV. SECTION 4: APPLICATIONS OF STEM CELLS IN MEDICAL SERVICES

The remarkable ability of stem cells to differentiate into diverse cell types throughout the human body has positioned them as a versatile and cutting-edge tool for a range of medical applications, including gene therapy, tissue and organ regeneration, and the treatment of chronic ailments. Stem cells hold great promise for improving the overall well-being of individual patients on a global scale. This section highlights some of the clinical, economic and research applications of stem cells for their potential therapeutic benefits (**Figure 9**).

Figure 9. Stem cells applications for medical services

1. RESEARCH APPLICATIONS

Stem cells are of great interest in biomedical research because of their unique ability to self-renew and differentiate into different cell types. These properties make stem cells promising for the treatment of chronic and degenerative diseases. In addition, stem cells have also proven to be useful in research to better understand the biology of development and disease, as well as for the identification of new therapies. The areas of application in stem cell research are as follows:

1.1. **Developmental biology research:** Stem cell data can be used to investigate developmental biology, such as cell differentiation and tissue regeneration. For example, stem cells can be used to study the development of the nervous and immune systems, amongst others.

1.2. **Development of medical treatments:** Stem cells are used to develop medical therapies to treat a wide variety of diseases and injuries, such as heart disease, spinal cord injuries, and neurodegenerative diseases, amongst others.

1.3. **Study of diseases:** Stem cells are used to investigate human diseases, which helps to better understand how they develop and how they can be treated more effectively. Scientists can use stem cells to study specific diseases in the laboratory, allowing them to conduct more precise research.

1.4. **Toxicity testing:** Stem cells are also used to test the toxicity of chemicals and drugs in the human body. This allows scientists to determine whether a chemical or drug is safe for use in humans before conducting clinical trials.

1.5. **Tissue and organ regeneration:** Stem cells are used in tissue and organ regeneration, which can help treat injury and disease. For example, stem cells can be used to create new heart or nerve cells that are used to repair damaged tissues.

1.6. **Identifying new drugs**: Stem cells can be used to identify new drugs that can treat specific diseases. Scientists can use stem cells to study how drugs interact with cells in the human body and how they may affect health.

1.7. **Disease research:** Stem cell data can be used to investigate the causes and mechanisms of diseases. For example, stem cells can be used to study diseases such as cancer, diabetes, and Alzheimer's disease**.**

1.8. **Healthy Aging focus:** Stem cells possess properties that may prevent and delay the detrimental effects of aging. Scientific studies have shown that these cells can reduce inflammation, performing immunomodulatory functions, regenerating tissues, and counteracting oxidative stress. These abilities are the result of their considerable plasticity, their capacity for self-renewal and their ability to differentiate in different directions.

1.9. **Stem cell rejuvenation**: This ***experimental*** approach is being investigated to overcome the inherent effects of natural aging by using a high concentration of young stem cells administered to the patient

by intravenous injection. These recently incorporated cells could replace "aged" cells, allowing the body to function more efficiently. Currently, it should be considered only in the context of clinical trials.

2. CLINICAL APPLICATIONS

Clinical data obtained from stem cell therapies has several important applications in regenerative medicine and biomedical research. Some of these applications include**:**

2.1. **Evaluation of the safety and efficacy of stem cell therapies:** Clinical data from clinical trials is essential for determining whether stem cell therapies are safe and effective for treating diseases and injuries. This data can help researchers determine what doses of stem cells are safe and what the best method of administration is.

2.2. **Identification of new therapeutic indications:** Clinical data from stem cell therapies can also provide valuable information about new therapeutic indications for disease treatment. For example, clinical data from stem cell therapies for the treatment of heart disease can help identify new therapeutic indications for other cardiovascular diseases.

2.3. **Development of new therapeutic products:** Clinical data can also help researchers develop new therapeutic products based on stem cells. For example, clinical data from stem cell therapies can be used to develop combination therapies with other treatments, such as gene therapy.

2.4. **Identification of biomarkers**: Clinical data from stem cell therapies can also help identify novel biomarkers that have the potential to predict treatment response or identify patients who may be more likely to respond better to a specific therapy.

2.5. **Regenerative medicine:** Focuses on using cellular and molecular therapies to repair or replace damaged or diseased cells, tissues, and organs. Another approach is to use stem cells to generate new tissues and organs.

2.6. **Hematopoietic cell transplantation:** It may be an allogeneic or autologous transplant in which healthy hematopoietic stem cells are transferred to a recipient to replace damaged or diseased cells in the recipient's bone marrow. This procedure is commonly used to treat certain types of blood cancers and other immune system disorders.

Other aspects for clinical applications that healthcare facilities and other parties should consider:

2.7. The appropriate balance between risk and benefit in using stem cell-based treatment when assessing new interventions for diseases that are rare, life-threatening, or have progressed despite the use of all currently available conventional therapies, according to institutional committees' approval. In addition, all products must have substantial evidence of safety and efficacy before being marketed to patients.

2.8. To ensure patient safety and confirm the therapeutic benefit of a product, it is imperative that product developers collect, analyse, and report safety and efficacy data to identify adverse events. Regulatory oversight plays a critical role in overseeing post-approval studies and ensuring compliance with safety protocols.

3. COMMERCIAL APPLICATIONS AND MANUFACTURE

The manufacturing of clinical treatments with stem cells is a complex process that requires rigorous evaluation of quality and safety. Therefore, advances in the manufacturing of clinical treatments with stem cells have great potential for the development of new therapies and for improving the quality of life of patients with various diseases:

3.1. **Cell culture:** The manufacturing of clinical treatments with stem cells involves obtaining, culturing, and expanding stem cells for therapeutic use. Therefore, one of the main consequences of stem cells in manufacturing is the culture and expansion of stem cells.

3.2. **Cell differentiation**: Stem cells could differentiate into different cell types, making them a useful tool for producing specialized cells for the treatment of various diseases. In the manufacturing of clinical treatments, stem cells are differentiated into specific cells, such as neurons or blood cells, for therapeutic use.

3.3. **Tissue engineering:** Stem cells are also used in the manufacturing of clinical treatments through tissue engineering. In this process, stem cells are used to create artificial tissues or to repair damaged or diseased tissues in the body.

3.4. **Production of cellular therapies:** Stem cells are used to produce cellular therapies, which are cell-based treatments used to treat various diseases. In the manufacturing of cellular therapies, stem cells are used to produce specialized cells for use in the treatment of diseases.

Other aspects for commercial applications and manufacture that healthcare facilities and other parties should consider:

3.5. The conditional approval of a stem cell-related product should be accompanied by a robust post-marketing surveillance system to promptly withdraw the product from the market if necessary.

3.6. In the case of stem cell-related products targeting rare diseases, clinical trials may be insufficient to determine efficacy, and thus producers should consider conditional marketing with the intention of conducting post-approval studies to confirm safety and efficacy.

3.7. The expense of treatment should be accessible for patients to obtained stem cell-based interventions.

4.Relevant References Documents

No.	Reference Date	Reference Name	Relation Explanation / Coding / Publication Links
1	**2021**	EU Regulation 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation).	Wolford, B. What is GDPR, the EU's new data protection law? - GDPR.eu. [online] GDPR.eu. Available at: https://gdpr.eu/what-is-gdpr/> [Accessed 7 July 2021
2	**2020**	Regulating the unknown: a guide to regulating genomics for health policymakers.	European Observatory on Health Systems and Policies, Williams, Gemma A, Liede, Sandra, Fahy, Nick, Aittomaki, Kristiina. et al. World Health Organization. Regional Office for Europe. https://apps.who.int/iris/handle/10665/338975

3	**2021**	Guidelines for Stem Cell Research and Clinical Translation	International Society for Stem Cell Research (ISSCR). (2021). https://static1.squarespace.com/static/611faaa8fee682525ee16489/t/62ed69b184e2ed258e6eb7e4/1659726257773/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf
4	**2011**	The Stem Cell Laboratory: Design, Equipment, and Oversight	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3695816/pdf/nihms468057.pdf
5	**2021**	Machine Learning in Stem Cells Research: Application for Biosafety and Bioefficacy Assessment	https://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=9344621
6	**2016**	NIH Stem Cell Information [World Wide Web site]. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services, 2016	https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research
7	**2006**	Indian Council of Medical Research. *Ethical Guidelines for Biomedical Research on Human Subjects. Indian Council of Medical Research.* 2006.	http://www.icmr.nic.in/ethical_guidelines.pdf .
8	**2017**	Indian Council of Medical Research. *National Guidelines for Stem Cell Research.* 2017.	http://www.icmr.nic.in/guidelines/Guidelines_for_stem_cell_research_2017.pdf .
9	**2018**	Guidelines for Human Stem Cell Research Pursuant to Health and Safety Code §125118	https://www.cdph.ca.gov/Programs/CFH/DMCAH/HSCR/CDPH%20Document%20Library/HSCR-StemCellResearchGuidelines.pdf
10	**2016**	NIH Guidelines for Human Stem Cell Research	https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research
11	**2021**	Quality Management and Accreditation in Hematopoietic Stem Cell Transplantation and Cellular Therapy	https://www.ncbi.nlm.nih.gov/books/NBK584278/#!po=12.5000
12	**2020**	Council of Ministers' Decision No. (6) of Near 2020 on Endorsement of the Regulations of Cord Blood and Stem Cells Storage Centers	https://mohap.gov.ae/app_content/legislations/php-law-en-97/mobile/index.html
13	**2018**	What Are "Biologics" Questions and Answers - FDA	https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers

14	**2017**	FDA Glossary and terms	https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#D

5. Appendices

Classification and Sources of Stem Cells - Stem Cell type and potential use.

Stem Cells Type	Source	Stem Cells Potential	Example Use
Totipotent	Zygote and morula (early embryonic stages)	Can develop into a complete organism including both embryonic and extraembryonic cell types.	Potential in therapeutic cloning and regenerative medicine, although currently highly controversial and not practiced.
Pluripotent	Inner cell mass of the blastocyst induced pluripotent stem cells (iPSCs).	Can differentiate into all three germ layers (endoderm, mesoderm, and ectoderm), but cannot form an entire organism.	iPSCs can be used in regenerative medicine to treat diseases such as Parkinson's, diabetes, and spinal cord injuries by replacing damaged or lost cells.
Multipotent	Hematopoietic stem cells in bone marrow, neural stem cells in the brain, mesenchymal stem cells in bone marrow and adipose tissue.	Can differentiate into a number of cells, but only within a particular lineage.	Hematopoietic stem cells are used in bone marrow transplants to reconstitute a patient's immune system; mesenchymal stem cells are used in experimental treatments for a range of conditions including heart disease and orthopedic injuries.
Unipotent	Muscle stem cells, basal cells in the skin	Can only differentiate into their associated cell type.	Skin stem cells are used in skin grafts for burn victims; muscle stem cells are studied for potential treatments of muscle wasting diseases.