Standards for Autologous Adipose-Tissue Derived Stem Cells/Stromal Vascular Fraction Cells (ADSCs/SVFCs) Therapy

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INTRODUCTION

Dubai Health Authority (DHA) is a governing entity that is responsible to oversee the Health System in the Emirate of Dubai. DHA was formed in 2007 under the Directive of Sheikh Mohammed bin Rashid Al Maktoum, the Vice President, Prime Minister and Ruler of Dubai. Health Regulation Sector (HRS) of Dubai Health Authority (DHA) is the responsible entity for regulating, licensing and monitoring health facilities and healthcare professionals in the Emirate of Dubai. HRS aims to fulfil the following overarching DHA Mission to 'Transform Dubai into a leading healthcare destination by fostering innovative and integrated care models and Strategic Programs 1 and 7:

1.4: Introduce innovative medical technologies in the provision of healthcare services

1.5: Promote innovation culture

7.1: Innovate in the delivery of diabetes treatment

9.1 Enhance the value proposition and targeting operating model for all providers in Dubai

9.2 Revise and update regulations and policies

9.4 Improve the Medical Tourism Ecosystem

The Standard for Autologous Adipose Tissue Derived Stem Cells/Stromal Vascular Fraction Cells (ADSCs/SVFCs) therapy was development to improve the safety and quality of services in the Emirate of Dubai. The document sets out the minimum Standards to be met for manufacturing, collection, processing, testing, storage and use for minimally manipulated autologous, same day use of ADSCs/SVFCs for therapeutic purposes.

ACKNOWLEDGMENT

The Standard was developed by the Health Policy and Standards Department (HPSD) and reviewed by The Dubai Scientific Board for Stem Cell Therapy and Subject Matter Experts. HRS would like to acknowledge and thank these professionals for their dedication toward improving the quality and safety of healthcare services in the Emirate of Dubai.

Health Regulation Sector

Dubai Health Authority

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EXECUTIVE SUMMARY

The use of stem cells has undoubtly proliferated over the past decade primarily due to the rising burden of disease and quest to improve quality of life and life expectancy. The growing interest in Autologous Adipose Tissue Derived Stem Cells/Stromal Vascular Fraction Cells (ADSCs/SVFCs) mimics that of the Platlet Rich Plasma (PRP) therapy era. The primary interest has been due to its anti-apoptotic, anti-inflammatory, pro-angiogenic, immunomodulatory, and new tissue properties, which make them effective or alternative options in plastic surgery, regenerative medicine and medical therapies and diseases of unmet clinical need. Furthermore, the process for harvesting ADSCs/SVFCs through subcutaneous lipo-aspiration is generally less painful than traditional bone marrow extraction, done under local anesthesia and does not lead to ethical concerns on the use of embryonic and perinatal stem cells. Stem cells can potentially develop into various cell types and tissues throughout the lifespan of a person and occur naturally as an internal repair system to rejuvenate and alleviate inflammation as has been seen as a last resort therapy for certain chronic conditions and diseases of unmet clinical need. In such circumstances, understanding the state of disease pathology is critical to understanding when SVFCs would be most beneficial as neither surgery nor use of medication results in healing of body tissues. Research on stem cells continues to evolve the field of medicine and is one of the most exciting areas of contemporary biology, but as with many expanding fields of scientific inquiry, new questions arise on the therapeutic benefits and as new discoveries are found.

The Standard sets out the requirements to provide Autologous Adipose Tissue Derived Stem Cells/Stromal Vascular Fraction (ADSC/SVFCS) Therapy. Application of Autologous ADSCs/SVFCS is understood to be relevant to the field of plastic surgery and as last resort therapy for certain chronic conditions. ADSCS/SVFCS have not yet been accepted the standard of care and should only be offered in cases where conventional medical treatments have not been successful or where there's particular knowledge that cell therapy would be the best alternative based upon data collection and understanding of pathology, where the risk of surgery is high or in circumstances where the patient does not want invasive surgery. In such circumstances, the patient must fully understand the risks and consent for such therapy. Healthcare providers are required to fully comply with the Federal and local laws and regulations and DHA facility, professional and service licensure requirements set out in this Standard and avoid the use of exaggerated, alarming expressions and/or unfounded claims for such therapies.

DEFINITIONS

Adipose Tissue-Derived Stem Cells (ADSCs) are mesenchymal cells with the capacity for self-renewal and multi-potential differentiation. This multi-potentiality allows them to become adipocytes, chondrocytes, myocytes, osteoblasts and neurocytes among other cell lineages.

Autologous: Means the transplantation, implantation, infusion or transfer of cells (human) or tissue into the individual from whom the cells or tissue were received.

Autologous Minimal Manipulation: Cell(s) that have undergone isolation of human adipose tissue with ultrasound or GMP collagenase approved for use in the UAE (or other means approved by UAE) where this does not affect their inherent biological properties, function or characteristics of the cell. Human Cells, Tissues and Cellular/Tissue-Based Products (HCT/Ps) characteristics of the cell remain intact and they are in their original form no more than minimally manipulated for processing (relates to the nature and degree of processing), and is not combined with another article, antibiotic or enzyme except for water or sterilization agent and neither of these lead to a clinical safety concern with respect to the HCT/P.

Good Tissue Practice: include those requirements set out by the FDA that directly relate to cell preparation and preventing the introduction, transmission, or spread of communicable disease by HCT/Ps and includes requirements for health facilities and laboratories, environmental controls, infection controls, aseptic technique, sanitation and sterilization, supplies and reagents, recovery, equipment, processing controls, validation testing, administration of tissue, labelling and tracing controls and temporary storage. These practices

may vary depending upon whether cells are prepared in laboratory setting or during a surgical procedure.

Mesenchymal stem cells: Are multipotent stromal cells which have the potential to separate into a range of different cells such as bone cells (osteoblasts), cartilage cells (chondrocytes), muscle cells (myocytes) and fat cells (adipocytes) which give rise to marrow adipose tissue. Studies have shown MSCs to be present in ADSCs. They may also effect changes via paracrine effects (e.g. donating necessary parts to "struggling" cells).

Same day procedure: Refers to same surgical procedures are those that involve an incision or instrumentation during which an HCT/Ps are removed from and implanted into the same individual within a single operation performed at the originating or receiving DHA Licensed Health Facility, and not stored for another appointment, procedure or day. In some cases, cells may be transported to facilities (e.g. radiology labs) the same day for image guided injections.

Stromal Vascular Fraction (SVFCs): Derived from adipose tissue contains heterogeneous cell populations such as mesenchymal progenitor/stem cells, preadipocytes, endothelial cells, pericytes, T cells, and M2 macrophages and ADSCs. SVFCS-derived mesenchymal progenitor/stem cells and can be deployed during point of care procedures. They can be expanded in vitro and have the potential to create diverse lineages of cells.

ABBREVIATIONS

ADSCs: Adipose-Tissue Derived Stem Cells

AMM: Autologous Minimally Manipulated

FDA: Food and Drug Administration

CGTP: Current Good Tissue Practice

GMP: Good Manufacturing Practice

HCT/P: Human Cells, Tissues, and Cellular and Tissue-Based Products

MSC: Mesenchymal Stromal/Stem Cells

SVFCs: Stromal Vascular Fraction

BACKGROUND

Regenerative medicine has the promise of repairing damaged tissues and organs and restoring functionality by stimulating the body's own regenerative capacity. The interdisciplinary field comprises several techniques and specialties, such as tissue engineering, medicine and molecular biology, to replace, engineer, or regenerate cells, tissues, or organs with the objective of restoration or establishing of the normal bodily functions. Different cell types have been investigated for their viability in regenerative medicine; including adult Mesenchymal Stem Cells (MSC). MSC have been known for over half a century to have the potential to develop into various cell types throughout the lifespan of a person and MSC have numerous applications in the medical and biomedical science fields, including the treatment of acute and chronic diseases and regenerative medicine therapy because they can differentiate into a variety of different cell lineages or positively affect struggling cells via a paracrine effect. ADSCs/SVFCs have similar characteristics to MSC with the potential to differentiate into cells of mesodermal origin, such as adipocytes, cartilage, bone, and skeletal muscle, as well as cells of non-mesodermal lineage, such as hepatocytes, pancreatic endocrine cells, neurons, cardiomyocytes, and vascular endothelial cells. In addition, ADSCs possess anti-apoptotic, anti-inflammatory, pro-angiogenic, immunomodulatory, and new tissue properties, which makes them effective in plastic surgery, regenerative medicine and medical therapies. Improvements in fat grafting techniques to correct facial and breast reconstruction have historically been based on the enrichment of the graft with autologous Adipose-Tissue, platelet-derived growth factors, hormones, and insulin. However, refinements in extracting and harvesting ADSCs

through Stromal Vascular Fraction (SVFCs) have made it possible to increase the number and efficacy of cells. Thus, Adipose tissue is no longer considered an energy reservoir, thermal insulator or mechanical buffer, but rather therapeutic for endocrine, nervous and cardiovascular systems. The advantages of ADSCs include the greater ease of tissue access and harvesting by means of subcutaneous lipo-aspiration, a much less painful procedure than harvesting bone marrow stem cells, and their use is not associated with ethical controversies observed with Embryonic Stem Cells because they are harvested from autologous adipose tissue. Furthermore, the extraction of ADSCs through the process of liposuction aspiration is a relatively safe procedure.

The stem cell extraction procedure is based on the separation of the Stromal Vascular Fraction (SVFCS) contained within adipose tissue. Isolation of ADCSs can be achieved by mechanical dissociation by liposuction, with the use of enzyme to free the human adipose cells from their protein bonds (i.e. GMP collagenase approved for use in the UAE) or by rapid sonication (sonication-mediated cavitation) and possibly other FDA techniques being developed. Thereon, stem cells produced in an off-site laboratory undergo sterility and cell count and viability check before being prepared for administration back into the patient. The manufacturing process must follow CGTP.

1. PURPOSE

1.1. To maximise the safety and quality of ADSCs therapy in Dubai Health Authority (DHA) licensed health facilities.

2. SCOPE

2.1. ADSCs therapy in DHA licensed health facilities.

3. APPLICABILITY

3.1. DHA licensed healthcare professionals and health facilities authorised to provide ADSCs Therapy.

4. STANDARD ONE: REGISTRATION AND LICENSURE PROCEDURES

4.1. All health facilities providing ADSCs Therapy shall adhere to related UAE Federal and Local Laws and Regulations.

4.1.1. Facilities that are new or require significant refurbishment should comply with the requirements sets out in the DHA Health Facility Guidelines (HFG).

4.2. Licensed health facilities opting provide ADSCs Therapy services shall inform Health Regulation Sector (HRS) and apply to for licensure and authorisation to provide the required service through DHA website: https://www.dha.gov.ae.

4.3. ADSCs Therapy services shall only be performed in a Hospital or Day Surgical Centre or Clinic setting that fulfils the requirements set out in the Standard.

4.3.1. Extraction of ADSC is only permitted in a Hospital, Specialty Hospital or Day Surgical Centre setting.

5. **STANDARD TWO:** HEALTH FACILITY REQUIREMENTS

5.1. The health facility shall have in place written documentation for the following:

5.1.1. Service description.

5.1.2. Scope of services.

5.1.3. Staff job descriptions.

5.1.4. Policy and procedure for end to end provision of ADSCs services to include but limited to:

a. Staffing requirements and their roles and responsibilities.

b. Clinical privileging, governance and reporting arrangements.

c. Patient acceptance and referral criteria.

d. Patient exclusion criteria.

e. Patient assessment, admission, management, discharge and follow up

f. Patient education and informed consent (English and Arabic).

5.1.5. Standard Operating Procedures for cellular therapy for Autologous Minimal Manipulation (AMM) that are approved by a DHA recognised clinical lab accreditor (refer to DHA Policy for Clinical Lab Accreditation):

5.1.6. Harvesting:

a. Marking site for tissue harvest.

b. Sterilisation and numbing.

c. Incision/puncture wound.

d. Administration of sub-dermal or tumescent anesthetic fluid.

e. Lipo-aspirate harvesting.

f. Cleansing and suturing.

g. Lipo-aspirate preparation/decanting.

5.1.7. Current Good Tissue Practice:

a. Clinical laboratory services.

b. Equipment monitoring and maintenance services.

c. Transfer of fat to sterile lab.

d. Placement of tissues in isolator hood or equivalent.

e. Ultrasonic sonication-mediated cavitation of specimen or methods of cell processing.

f. Cell washing.

g. Centrifugation.

h. Cell harvesting.

i. Cell filtration.

j. Cell count testing and viability.

k. Cell sample sterility testing.

l. Tissue labelling and tracing.

m. Cell insertion to patient (intravenous or site specific).

5.1.8. Infection control and prevention measures for communicable diseases (infection disease testing for laboratory processed cells).

5.1.9. Managing patient health records.

5.1.10. Incident reporting.

5.1.11. Patient privacy and confidentiality.

5.1.12. Medication management.

5.1.13. Emergency action plan.

5.1.14. Patient discharge/transfer/follow up.

5.1.15. Transfer of critical/complicated cases when required.

5.1.16. Complaints procedure.

5.1.17. Laundry services.

5.1.18. Housekeeping services.

5.1.19. Hazard waste management.

5.1.20. Medical waste management to meet Dubai Municipality (DM) requirements.

5.2. The Health Facility shall:

5.2.1. Maintain a Charter of patients' Rights and Responsibilities posted at the entrance of the premise in two languages (Arabic and English).

5.2.2. Make available printed patient information leaflets (or online) of available therapies including risks and alternatives to support informed decision-making.

5.2.3. Ensure there is adequate lighting and utilities, including environmental and temperature, humidity, ventilation controls and air filtration, water taps, medical gases, sinks and drains, lighting, and electrical outlets.

5.2.4. Install and operate required equipment in accordance to the manufacturer's specifications/biomedical certification.

5.2.5. Ensure safe and easy access to the health facility and treatment areas for all patient groups.

5.2.6. Ensure healthcare professionals are trained as per the scope of practice and services provided including the ability to manage critical and emergency cases.

5.2.7. Clearly define consent for investigations and ADSCs therapies.

5.2.8. Fulfil DHA health facility and lab requirements for accreditation as per DHA Policy requirements.

5.2.9. Fulfil the reporting requirements set out by DHA or through its nominated body.

5.2.10. Ensure there are written procedures for all surgical procedures in the facility involving adipose tissue aspiration.

5.2.11. Ensure there are written procedures for all non-surgical procedures in the facility involved in the process of the stem cell regenerative therapy.

6. **STANDARD THREE:** HEALTHCARE PROFESSIONALS REQUIREMENTS

6.1. Autologous Adipose-Tissue Derived Stem Cell Stem Cell/SVFCS therapy shall only be provided by:

6.1.1. A DHA licensed physician working under the supervision of a consultant in related field.

6.1.2. The physician must be certified in the appropriate field with evidence of recognized training in ADSCs therapy with clear description on the amount and the nature of the hands-on training received, including:

a. Donor selection.

b. The selection of procedures.

c. The preparation of patients.

d. Screening for infectious diseases.

e. Maintenance of asepsis in non-hospital settings.

f. Intra-operative patient monitoring.

g. Post-operative care and follow-up.

h. Quality improvement in surgical services.

i. Hands-on training in the surgical technique for liposuction.

j. Fluid and electrolyte balance, potential complications of ADSCs Therapy.

k. Processing and delivery of the aspirate.

l. Have certified training in regenerative medicine with experience in liposuction/aspirate resulting in demonstrated competency.

    i. Training for regenerative medicine should include a minimum of 30 cases.

m. Have evidence of satisfactory performance of ADSCs Therapy procedures.

n. Have evidence of Continuous Medical Education in ADSCs/SVFCS (CME 25) per year.

o. Hold an Advanced Cardiac Life Support (ACLS) or Advanced Life Support (ALS) certification.

6.2. The Clinical Privileging Committee and/or Medical Director of the health facility shall privilege the physician as per section 7. The privilege shall be reviewed and revised as per DHA Policy for Clinical Privileging.

6.3. Regenerative Physicians shall:

6.3.1. Be supported by a minimum of one (1) perioperative Registered Nurses (RNs) for each ADSCs Therapy procedure and one (1) lab technician.

a. RNs and lab technician assisting in ADSCs Therapy shall be knowledgeable and trained in the different aspects of the ADSCs Therapy, aseptic fields and instruments, proper use of equipment, appropriate patient monitoring, assisting in emergency procedures and where necessary the nurse shall assist in cardiopulmonary resuscitation if required.

b. The registered nurse must be continuously in attendance of the patient until discharge shall have documented training and experience with:

i. Procedural Technique (collection, Isolation and administration).

ii. Monitoring and documentation of vital signs.

iii. Maintaining aseptic fields and instruments.

iv. Assisting emergency procedures in addition to the use of a bag-valve-mask device and current certification in cardiopulmonary resuscitation/AED use.

v. Medical device reprocessing and infection control measures.

vi. Assembly, calibration, programming and operation of equipment.

c. All lab technicians must be DHA licensed operating within the lab and must undergo training and certification in accordance prior to performing any autologous ADSCs related tissue handling and processing:

i. Training shall include at least three (3) successful outcomes of ADSCs processing, sterility testing and cell count viability.

ii. Training must be signed off by the DHA Licensed Medical Director and Treating Physician with speciality in Regenerative Medicine.

iii. Training shall be undertaken on an ongoing basis to assure compliance with set quality standards.

7. **STANDARD FOUR:** PERMITTED THERAPIES FOR AUTOLOGOUS ADSCs

7.1. Only Autologous Stem Cell Therapy/Stromal Vascular Fraction (SVFCS)/Adipose-Derived Regenerative Cells (ADRCs) is permitted and the following criteria must be met:

7.1.1. Removal and implant of the HCT/Ps is done to the same individual from whom they were removed (autologous use);

7.1.2. Minimally manipulated;

7.1.3. The HCT/P does not have an effect on the body as a whole and is not reliant upon the metabolic activity of living cells for its primary function;

7.1.4. Implanted HCT/Ps is conducted within the same surgical procedure;

7.1.5. The communicable disease and safety risks, generally would be no different from those typically associated with surgery; and

7.1.6. Cell preparation follows Current Good Tissue Practice (CGTP).

7.2. Permitted Therapies are limited and shall be explained to patients in the context that they are not yet the Standard of Care, only offered where first line therapies and conventional medical treatments have not been successful, where there's particular knowledge that cell therapy would be the best solution based upon data collected and understanding of pathology, where the risk of surgery is high or in circumstances or in cases where the patient does not want invasive surgery. It is not meant to be an alternative for antibiotics or necessary surgery though it may serve as a useful adjunct to optimize healing. In such circumstances, the patient must fully understand the risks

and provide written consent for ADSCs therapy. The safety and scientific validity of ADSCs therapies remains the responsibility of health facility management and the treating physician:

7.2.1. Category 1-2 - Degenerative and Neurological Autism, Multiple Sclerosis, Parkinson's, Cerebral Palsy, Concussion, Traumatic Brain Injury, Chronic Traumatic Encephalopathy, Alzheimers and Immunosenescence - SHALL ONLY be provided as part of a Clinical Trial approved by DHA ethics committee and medical director of the health facility where the service is provided.

a. All clinical trials must be registered on https://www.clinicaltrials.gov/
b. Clinical trial exemption criteria may be submitted to DHA Medical Education and Research Department for a decision to include:
    i. Preliminary clinical evidence (not necessarily clinical trial) demonstrates its effectiveness through reliable and validated tools and shows consistency and persuasiveness of positive outcomes.
    ii. The numbers for effectiveness are statistically significant and represent the treating population.
    iii. The treatment demonstrates the product has the potential to address specified unmet medical need for a serious condition.
    iv. There are no other known scientific evidence based treatments for the condition or disease.

v. The rate of incident (adverse event) is no greater than comparable available evidence-based treatments.

vi. Evidence of treatment success is available on a transparent online registry.

vii. There is validated patient experience data at 6-12 months to demonstrate effectiveness with minimal side effects.

viii. Any other requirements requested by DHA.

7.2.2. Category 3 - Osteoarthritis, Chronic inflammation, Diabetes Mellitus, CVD and COPD – Requires DHA licensure and DHA ethics committee approval and medical director of the health facility where the service is provided.

a. Where evidence or a transparent registry demonstrates the need, special techniques including but not limited to CT guided injections, fluoroscopy, or ultrasound should be used to maximize the effectiveness of the treatment site.

7.2.3. Category 4 - Cosmetic and skin rejuvenation – Requires DHA licensure approval for ADSCs and approval from the medical director of the health facility where the service is provided.

7.3. Advertising of ADSCs therapies shall only be permitted to the DHA licensed Health Facility and Physician. Use of third-party logos may be permitted upon mutual and written agreement and will be subject to the competent regulatory authority(s) approval for health advertisement.

7.3.1. All advertising must make use of the Physicians title as per DHA license.

7.3.2. All advertising must indicate the treatment as an alternative option to the standard of care.

7.3.3. All advertising must comply with DHA Guidelines for advertisement and not utilize any exaggerated/alarming expressions/unfounded terms such as or equivalent to unique, one of a kind, the best, safest, the only, the first, incomparable, unprecedented, best product, imitates, magic, miraculous, assured success, very limited quantity or opportunity, seize the opportunity, guaranteed, pain free, safe, has no side effects, get your money back, 100% and immediate results.

8. **STANDARD FIVE:** SAFETY & QUALITY REQUIREMENTS FOR AUTOLOGOUS ADSCs

8.1. A quality and safety program for Current Good Tissue Manufacturing and tracking of HCT/Ps must be in place and reviewed frequently to detect and prevent adverse or sentinel events and transmission of communicable diseases. The quality program must:

8.1.1. Include a nominated lead for Quality Assurance and Quality Control.

8.1.2. Incorporate Current Good Tissue Practice into Standard Operating Procedures.

a. Ensure documented and appropriate action is taken when Good Tissue Practice requirements are not met.

8.1.3. There must be in place a system for contact tracing of cells used.

8.1.4. Assure infection control and sanitation is met to the highest standards.

8.1.5. Ensure only licensed, trained and privileged staff are engaged in ADSCs therapies, reporting and investigation of complaints and adverse and sentinel events.

a. Staff training and education needs must be documented and up to date.

b. Changes in staffing must be documented and all clinical privileging requirements must be met confirmed by the Medical Director or the Privileging committee as per DHA Policy prior to issuance of privileges for service provision of ADSCs.

8.1.6. Form part of the facility and lab accreditation program.

8.1.7. Ensure clinical audits are conducted twice a year with a documented improvement plan.

8.1.8. Take corrective action when Standard Operating Procedure requirements are not met.

8.2. The location/room for ADSCs therapy is specified to reduce the risk of infection, contamination, improper labelling and tracing.

8.2.1. Aseptic locations for assessment, extraction/recovery, preparation and harvesting and reinsertion or infusion of cells must be included as part of safety and the quality control program.

8.2.2. Isolation of ADSCs shall only be conducted in a sterile point of care setting or lab setting.

a. All settings must follow comprehensive cell processing, infectious disease control, labelling and cell transfer protocols.

8.2.3. Lab setting can be used to service other healthcare providers under same day procedure and include accurate cell count.

8.3. Ensure documentation of environmental monitoring of temperature, filtration, humidity and equipment is maintained on a regular basis.

8.4. Ensure measures taken to assure sterility, infection control, and minimisation of microbiological contamination and/or transfer of communicable diseases during extraction/harvesting, manufacturing, handling, storage and administration of stem cells through strict lab policy and procedures/protocols and quality control and compliant with manufacturer recommendations.

8.5. Maintain up to date records of all equipment cleaning, sanitisation, calibration, use and disposal.

8.6. Equipment must be calibrated on a regulation basis with supporting documentation.

8.7. Have clear written protocols to ensure the validation of labels, tests or results or procedures and their times are accurate as per pre-determined standards.

8.7.1. Deviations from these standards must be documented in addition to actions taken to rectify identified shortfalls.

8.8. Validation testing and study must be conducted and documented on a regular

basis to include but not be limited to:

8.8.1. Testing for microorganisms.

8.8.2. Preparation.

8.8.3. Sterilization.

8.8.4. Cleansing.

8.8.5. Temporary storage and removal of cells for insertion.

8.9. Use of mechanical or software for tissue extraction, harvesting, preparation or counting must be included in the validation testing.

8.10. Maintain up to date records of all supplies and reagents used for ADSCs therapy.

8.11. Supplies and reagents must be registered by the Ministry of Health and Prevention and authorised by the health facility for use.

8.12. Use of growth factors, hormones or enzymes (excluding GMP collagenase for human adipose cell isolation approved for use in the UAE) to enhance or expand the number and/or efficacy of ADSCs from SVFCS or use of embryonic or amniotic or placenta or cord blood stem cells or any other form of stem cells in silo or combination with ADSCs is NOT permitted.

8.13. Sale, storage or use of ADSCs for any other person(s) who is not the 'same patient/individual' is NOT permitted.

8.14. A DHA licensed health facility seeking to transfer autologous ADSCs to another DHA licensed health facility for therapy must submit the following documentation to DHA for review and approval:

8.14.1. A Memorandum of Understanding between the two health facilities.

8.14.2. The originating facility has documented authorisation for ADSCs cell transfer through the practicing physician and medical director.

8.14.3. The receiving facility has documented authorisation for ADSCs cell transfer through the practicing physician and medical director.

8.14.4. The receiving heath facility have the necessary set up for ADSCs storage, use and infection control.

8.14.5. The conditions for cell transportation between two facilities can be met and strict patient documentation is in place from both the transferring and receiving health facility.

8.14.6. There is written consent from the patient for transfer of their ADSCs cells to the receiving facility for therapy for same day procedure.

8.14.7. The receiving heath facility evidences compliance to all relevant parts set out in the Standard for ADSCs therapy.

8.15. Pooling of ADSCs from one or more donors or for one of more procedures is NOT permitted.

8.16. Storage and cryopreservation of ADSCs beyond the same day same procedure is permitted upon patient written consent for up to 1 year only to maximise the efficacy and survival of ADSCs.

8.16.1. ADSCs prepared in the lab should be delivered in an accepted transport medium (hypothermic 2 - 8°C preservation medium) and transferred in a cool environment ready for syringe for deployment.

8.16.2. ADSCs should be used within a 2 hour period after preparation from surgery and no more than 4 hours at a controlled temperature.

8.16.3. Quality control and monitoring and back-up systems should be in place for cryopreservation in line with the latest medical practice and evidence for stem cell storage or ADSCs.

9. **STANDARD SIX:** PRE-OPERATIVE EVALUATION AND INFORMED CONSENT

9.1. A detailed medical history to account for any previous disease, drug intake and prior surgical procedures and screening of communicable diseases shall be undertaken for patients indicated for ADSCs Therapy.

9.1.1. Communicable Disease Screening shall include:

a. HCV Ab

b. HBs Ag

c. HIV Ag/Ab

9.1.2. Positive tests shall be reported the DHA Public and Protection Department.

9.2. Known contraindication(s) and risks shall be considered during clinical decision making and noted in the patient record which may include the following:

9.2.1. Medical conditions that may be aggravated by ADSCs or

anaesthesia.

9.2.2. Coagulopathies should be considered in the context of ensuring compression over the liposuction area is maintained 3-4 days following the procedure.

9.2.3. Medications that weaken haemostasis or that interact adversely with epinephrine.

9.2.4. Localised conditions of skin or subcutaneous tissue that make ADSCs Therapy hazardous (e.g. certain scars, hernias and injuries).

9.2.5. Significant skin laxity or deformity if several procedures are planned over the year.

9.2.6. Morbid obesity (patient that have a Body Mass Index (BMI) of 40 or more for Caucasians and 37.5 for Asians).

9.2.7. Psychological contraindications including but not limited to mood disorders, thought disorders, severe anxiety, or unrealistic expectations.

9.2.8. Active Cancer Patients.

9.2.9. Patients with infection, immune-compromised patients, and particularly, patients with active dental conditions that require treatment.

9.2.10. General anesthesia for children under the age of five years.

a. The Legal Guardian must provide informed consent.

b. A Paediatric Consultant, Paediatric Anaesthetist and a RN must be present during the procedure.

9.3. Physical evaluation of the patient should be comprehensive and documented. The evaluation should entail assessment of the patients general physical health and fitness for surgery. The site for ADSCs therapy should also be examined to check for potential problems.

9.4. Pre-operative testing should be performed to include haemoglobin level, blood counts, platelet counts, bleeding and clotting time, prothrombin and activated partial thromboplastin time, blood chemistry profile, infection and communicable disease.

9.5. All cases should be considered for:

9.5.1. Periodontal disease should be addressed prior to planned procedures.

9.5.2. Ultrasound examination and hormonal tests should be done for gynecomastia patients.

9.6. Other tests such as pregnancy test for women of childbearing age, liver function tests and electrocardiogram (ECG) and chest X-Ray for patients aged 50 years should be considered as appropraite.

9.7. Patient evaluation should be done in accordance with the standard of medical care such that the primary physician may be required to clear the patient and/or participate or consult in the patient's planned procedure.

9.8. The patient shall be provided with the consent form in advance of the procedure to review and ask questions prior to the procedure and issuance of informed consent.

9.8.1. Informed consent shall include an explanation in Arabic or English with supporting written educational material and discussion with patient and documentation in the patient records as a separate form.

9.8.2. Informed consent shall include details of the procedure, possible risks/complications and alternative treatment options.

9.8.3. Informed consent shall include the training and experience of the physician and supportive surgical team.

9.8.4. Informed consent should cover the following:

a. Comprehensive and accessible information concerning the diagnosis and procedure/surgery alternatives to ADSCs Therapy.

b. All usual and occasional side effects, risks and complications e.g. swelling, bruising, pain, seroma, haematoma, hyperpigmentation, infection.

c. Potentially life-threatening complications e.g. Fat Embolism Syndrome (FES), pulmonary oedema and necrotizing fasciitis sepsis, perforation of abdominal or thoracic viscera, cardia arrest, hypotension and haemorrhage.

d. Limitations of the procedure and if further procedures are needed for proper results.

e. The possibility of a poort surgical or cosmetical outcome.

f. The recovery duration and expected results.

g. The full cost of the procedure.

9.8.5. Informed consent shall be obtained from the patients their legal guardian if the patient is under 18 years or lack the full capacity to make a decision before the procedure/surgery is performed.

9.8.6. Minimum requirements for Patient and Physician Declaration/Consent are met as per **Appendix 1**.

9.8.7. All patients must be offered a cooling off period before surgery.

10. STANDARD SEVEN: INTRA-OPERATIVE MANAGEMENT

10.1. ADSCs Therapy should be limited between 60-120cc of total aspirant volume per procedure.

10.2. Larger volumes up to a maximum of 240cc of ADSCs may be undertaken with other procedures subject to additional necessary preoperative assessments under the direction of the treating physician.

10.3. Volumes greater than 60cc require cessation of anticoagulants and normal coagulation parameters.

10.4. Each ADSCs Therapy procedure must be conducted by a physician trained in regenerative medicine and supported by minimum of one (1) perioperative registered nurses who are trained and knowledgeable in the ADSCs Therapy procedure, safe tumescent drug concentrations or subdermal block, fluid management and appropriate patient monitoring by an RN and a lab technician for tissue processing.

10.5. All solutions should be prepared, labelled and signed by a qualified Registered Nurse (RN), physician or pharmacist using aseptic techniques and as per written protocols.

10.6. Intravenous access should be initiated prior to the procedure and maintained throughout, as needed.

10.6.1. Where IV is required, IV access should only be initiated prior to IV deployment.

10.6.2. Where IV access is deemed challenging, recommendations for special pre-op access should be considered.

10.7. Patients undergoing ADSCs Therapy shall be continuously evaluated with a pulse oximeter with audible signal recognition and an apparatus to measure blood pressure.

10.8. The physician shall perform incision, infiltration and aspiration.

10.9. Devices or drugs must be made immediately available and include a stethoscope, source of oxygen, self-inflating bag-valve-mask device and emergency crash cart.

10.10. DHA Health Facilities shall have a policy in place for management and transfer of patients in case of emergencies supported by a signed written transfer agreement with a nearby hospital to ensure timely transfer of complicated cases.

11. **STANDARD EIGHT:** POST-OPERATIVE CARE

11.1. There should be a dedicated RN in the recovery area who is trained (knowledgeable and skilled) to monitor vital signs, fluid and electrolyte balance and manage

potential complications of tumescent anaesthesia. The RN's sole responsibility shouldt be to monitor the patient post-operatively and follow emergency procedures until the patient is deemed well enought for discharge by the treating physician or the medical team.

12. STANDARD NINE: DISCHARGE AND OUTPATIENT FOLLOW UP

12.1. The health facility shall comply with the health facilities protocol for discharging patients and follow up after sedation/anaesthesia.

12.2. The health facility shall maintain written policies and procedures concerning the patient discharge, which reflect acceptable standards of practice and compliance with applicable regulations in the Emirate of Dubai.

12.3. Each patient discharge following ADSCs Therapy procedure shall receive a written discharge plan, in non-technical language, along with sufficient oral explanations to assist the patient and their nominated carer in understanding the plan and availability of outpatient services capable of meeting the patient's discharge needs.

12.4. All ADSCs patients shall be followed up by their treating physician for assessment of outcomes and reporting of Key Performance Indicators (KPIs).

13. STANDARD TEN: KEY PERFORMANCE INDICATORS

13.1. Key Performance Indicators shall be captured for each quarter and reported upon DHA request.

13.2. Submission will reflect outcomes achieved in the previous quarter.

13.3. The treating physician is required to maintain an update to date log of treatment and patient outcomes using validated tools (**tables 1 and 2**).

13.3.1. All efforts must be made and documented to follow up patients at 1, 3, 6 and 12 months intervals (**tables 1 and 2).**

13.3.2. Any serious adverse event – death, emboli, serious infection, serious event, hospitalization for any reason – should be reported to the DHA and logged on an internal registry within 48 hours of the event.

13.3.3. Follow-up reporting of the outcome(s) should occur as soon as necessary (after resolution of complications).

Table 1. Baseline Assessment

Patient ID	**Diagnosis**	**Date of intervention**	**Tool for Assessment** (e.g. pain score, biological testing, FLP, ADL, patient experience)	**Baseline Assessment**	**Treatment Method, dosage and start date** (site specific, intravenous/cc etc)	**Primary outcome measure**
Name and signature of Treating Physician: Name and signature of Medical Director:						

Table 2. Post Intervention Assessment

Patient ID	**1 month outcome**	**Adverse Event at 1 month** (No, if yes provide details)	**3 month outcome**	**Adverse Event at 3 months** (No, if yes provide details)	**6 month outcome**	**Adverse Event at 6 months** (No, if yes provide details)	**12 month outcome**	**Adverse Event at 12 months** (No, if yes provide details)
Name and signature of Treating Physician: Name and signature of Medical Director:								

REFERENCES

1. Alessandro Gennai et al (2017). Skin Rejuvenation and Volume Enhancement with the Micro Superficial Enhanced Fluid Fat Injection (M-SEFFI) for Skin Aging of thePeriocular and Perioral Regions. *Oculoplastic Surgery, Aesthetic Surgery Journal. 2017, Vol 37(1) 14–23.*
2. American Association of Blood Banks and Cellular Therapies (2019). Cellular Therapies Standards. 9th Edition.
3. Antunes MA, Lapa E Silva JR and Rocco PR (2017). Mesenchymal stromal cell therapy in COPD: from bench to bedside. *Int J Chron Obstruct Pulmon Dis. 2017 Oct 16;12:3017-3027. doi: 10.2147/COPD.S146671. eCollection 2017.*
4. Aronowitz JA, Lockhart RA and Hakakian CS (2018). A Method for Isolation of Stromal Vascular Fraction Cells in a Clinically Relevant Time Frame. *Methods Mol Biol. 2018;1773:11-19. doi: 10.1007/978-1-4939-7799-4_2.*
5. Arthur A, Zannettino A and Gronthos S (2009). The therapeutic applications of multipotential mesenchymal/stromal stem cells in skeletal tissue repair. *J Cell Physiol. 2009 Feb;218(2):237-45. doi: 10.1002/jcp.21592.*
6. Bacou F et al (2004) Transplantation of adipose tissue-derived stromal cells increases mass and functional capacity of damaged skeletal muscle. *Cell Transplant 13 103–111.*
7. Bateman ME et al (2018). Concise Review: Using Fat to Fight Disease: A Systematic Review of Nonhomologous Adipose-Derived Stromal/Stem Cell Therapies. *Stem Cells. 2018 Sep;36(9):1311-1328. doi: 10.1002/stem.2847. Epub 2018 Jul 16.*

8. Bowles AC et al (2017). Adipose Stromal Vascular Fraction-Mediated Improvements at Late-Stage Disease in a Murine Model of Multiple Sclerosis. *Stem Cells. 2017 Feb;35(2):532-544. doi: 10.1002/stem.2516. Epub 2016 Nov 9.*
9. Brown JC, Shang H, and Li Y (2017). Isolation of adipose-derived stromal vascular fraction cells using a novel point-of-care. device: cell characterization and review of the literature *Tissue Eng Part C Methods* 23(3) 125–135 https://doi.org/10.1089/ten. tec.2016.0377 PMID: 28177263
10. Bruun K et al (2018). Therapeutic applications of adipose-derived stem cells in cardiovascular disease. *Am J Stem Cells. 2018 Oct 1;7(4):94-103. eCollection 2018.*
11. Caplan AI (2007). Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol. 2007 Nov;213(2):341-7.*
12. Caplan AI and Correa D (2011). The MSC: an injury drugstore. Cell Stem Cell. *2011 Jul 8;9(1):11-5. doi: 10.1016/j.stem.2011.06.008.*
13. Centeno Christopher J et al (2010). Safety and Complications Reporting on the Re-implantation of Culture-Expanded Mesenchymal Stem Cells using Autologous Platelet Lysate Technique. *Current Stem Cell Research & Therapy, Volume 5, Number 1, 2010, pp. 81-93(13)* DOI: https://doi.org/10.2174/157488810790442796
14. Chae DS, Han S, and Son M, *et al* (2017) Stromal vascular fraction shows robust wound healing through high chemotactic and epithelialization property *Cytotherapy* 19(4) 543–554 https://doi.org/10.1016/j.jcyt.2017.01.006 PMID: 28209525.

15. Chamberlain G1, Fox J, Ashton B, Middleton J (2007). Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells. 2007 Nov;25(11):2739-49. Epub 2007 Jul 26.*
16. College of Physicians & Surgeons of Alberta (2018). Stem Cell Regenerative Therapy Standards & Guidelines, CSPA. Available on: http://www.cpsa.ca/wp-content/uploads/2018/02/Stem-Cell-Regenerative-Therapy-Standards.pdf (accessed 29/05/19).
17. Comella K et al (2017). Autologous Stromal Vascular Fraction in the Intravenous Treatment of End-Stage Chronic Obstructive Pulmonary Disease: A Phase I Trial of Safety and Tolerability. *J Clin Med Res. 2017 Aug;9(8):701-708. doi: 10.14740/jocmr3072w. Epub 2017 Jul 1.*
18. Comella K, Silbert R and Parlo M (2017). Effects of the intradiscal implantation of stromal vascular fraction plus platelet rich plasma in patients with degenerative disc disease. *J Transl Med. 2017 Jan 13;15(1):12. doi: 10.1186/s12967-016-1109-0.*
19. Comella K et al (2017). Safety Analysis of Autologous Stem Cell Therapy in a Variety of Degenerative Diseases and Injuries Using the Stromal Vascular Fraction. *J Clin Med Res. 2017 Nov;9(11):935-942. doi: 10.14740/jocmr3187w. Epub 2017 Oct 2.*
20. Dario Siniscalco et al (2018). Stem cell therapy in autism: recent insights. *Stem Cells Cloning. 2018; 11: 55–67.* Published online 2018 Oct 23. doi: 10.2147/SCCAA.S155410
21. Dinh-Toi Chu et al (2019). Adipose Tissue Stem Cells for Therapy: An Update on the Progress of Isolation, Culture, Storage, and Clinical Application. J *Clin Med. 2019 Jul;*

8(7): 917. Published online 2019 Jun 26. doi: 10.3390/jcm8070917. PMCID: PMC6678927, PMID: 31247996.

22. Eleni Oberbauer et al (2015). Enzymatic and non-enzymatic isolation systems for adipose tissue-derived cells: current state of the art. Oberbauer et al. *Cell Regeneration (2015) 4:7* DOI 10.1186/s13619-015-0020-0.
23. Foundation for the Accreditation for Cellular Therapy (2014). International Standards for Cellular Therapy. Available on: http://www.factwebsite.org/Standards/ (accessed on 29/05/19).
24. Farshid Guilak et al (2006). Colonal Analysis of the differentiation Potential of Human Adipose Derived Adult Stem Cells. *Journal of Cellular physiology 206;229-237.*
25. Food and Drug Administration (2011). Guidance for Industry. Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).
26. Food and Drug Administration (2016). New Direction Biosciences Scientific FDA Position Paper. Part 15 Hearing: Draft Guidances Relating To The Regulation Of Human Cells, Tissues, Or Cellular Or Tissue-based Products.
27. Food and Drug Administration (2017). Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception. Guidance for Industry

28. Food and Drug Administration (2018). Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff.
29. Food and Drug Administration (2018). CFR - Code of Federal Regulations Title 21.
30. Food and Drug Administration (2019). Expedited Programs for Regenerative Medicine Therapies for Serious Conditions. U.S. Department of Health and Human Services Food and Drug Administration, February 2019.
31. Fomekong E et al (2017). Application of a three-dimensional graft of autologous osteodifferentiated adipose stem cells in patients undergoing minimally invasive transforaminal lumbar interbody fusion: clinical proof of concept. *Acta Neurochir (Wien). 2017 Mar;159(3):527-536. doi: 10.1007/s00701-016-3051-6. Epub 2016 Dec 30.*
32. Francesco Simonacci, Nicolò Bertozzi, and Edoardo Raposioa (2017). Off-label use of adipose-derived stem cells. *Ann Med Surg (Lond). 2017 Dec; 24: 44–51*. Published online 2017 Oct 25. doi: 10.1016/j.amsu.2017.10.023.PMCID: PMC5671395PMID: 29123656
33. Gadelkarim M et al (2018). Adipose-derived stem cells: Effectiveness and advances in delivery in diabetic wound healing. *Biomed Pharmacother. 2018 Nov;107:625-633. doi: 10.1016/j.biopha.2018.08.013. Epub 2018 Aug 14*.
34. Gaidos Susan (2016). Cells from fat mend bone, cartilage, muscle and even the heart. Adipose tissue is a natural storehouse of healing cells. *FEATURE*

BIOMEDICINE,HEALTH CELLS. Available from: https://www.sciencenews.org/article/cells-fat-mend-bone-cartilage-muscle-and-even-heart (accessed 16/03/19)

35. Gentile P and Cervelli V (2018). Adipose-Derived Stromal Vascular Fraction Cells and Platelet-Rich Plasma: Basic and Clinical Implications for Tissue Engineering Therapies in Regenerative Surgery. *Methods Mol Biol. 2018;1773:107-122.* doi: 10.1007/978-1-4939-7799-4_9.
36. Gimble JM, Bunnell BA, Chiu ES, et al. Concise review: Adipose-derived stromal vascular fraction cells and stem cells: Let's not get lost in translation. *Stem Cells. 2011;29:749–754.*
37. Gnecchi, Massimiliano (2016). Mesenchymal Stem Cells (2008). Methods and Protocols. Methods in Molecular Biology.
38. Guo J et al (2015). Stromal vascular fraction: A regenerative reality? Part 2: Mechanisms of regenerative action. *J Plast Reconstr Aesthet Surg. 2016 Feb;69(2):180-8. doi: 10.1016/j.bjps.2015.10.014. Epub 2015 Oct 24.*
39. Haiko IMFL Pas et al (2017). Stem cell injections in knee osteoarthritis: a systematic review. Pas HIMFL, et al. *Br J Sports Med 2017*;51:1125–1133. doi:10.1136/bjsports-2016-096793
40. Harris David (2016). Long-term frozen storage of stem cells: challenges and solutions. *Journal of Biorepository Science for Applied Medicine. Published 7 July 2016 Volume 2016:4 Pages 9-20. DOI https://doi.org/10.2147/BSAM.S90142. University of Arizona*

Health Sciences Biorepository, Department of Immunology, Division of Translational Medicine, 4GMP Laboratory, University of Arizona, Tucson, 5Celebration Stem Cell Centre, Gilbert, AZ, USA.

41. Iyyanki T, Hubenak J and Liu J (2015). Harvesting technique affects adipose-derived stem cell yield *Aesthet Surg J* 35(4). 467–476 https://doi.org/10.1093/asj/sju055 PMID: 25791999 PMCID: 4532626
42. Jeffrey M. Gimble, Adam J. Katz and Bruce A (2007). Bunnell. Adipose-Derived Stem Cells for Regenerative Medicine. *Circ Res. 2007 May 11; 100(9): 1249–1260. doi:10.1161/01.RES.0000265074.83288.09.*
43. Jin Z et al (2015). Biological effects and mechanisms of action of mesenchymal stem cell therapy in chronic obstructive pulmonary disease*. J Int Med Res. 2015 Jun;43(3):303-10. doi: 10.1177/0300060514568733. Epub 2015 Apr 1.*
44. Joan Oliva, Arjie Florentino, Fawzia Bardag-Gorce and Yutaka Niihara (2019). Engineering, differentiation and harvesting of human adipose-derived stem cell multilayer cell sheets. *Regenerative Medicine 2019 March 4*
45. Khalpey Z, Janardhanan R, Konhilas J and Hemphill C (2014). First in man: adipose-derived stromal vascular fraction cells may promote restorative cardiac function. *Am J Med. 2014 May;127(5):e11-2. doi: 10.1016/j.amjmed.2013.12.024.*
46. Khalpey Z et al (2015). First in Man: Sternal Reconstruction with Autologous Stem Cells. *ASAIO J. 2015 Sep-Oct;61(5):e31-2. doi: 10.1097/MAT.0000000000000236.*

47. Koh YJ, Koh BI, and Kim H (2011) Stromal vascular fraction from adipose tissue forms profound vascular network through the dynamic reassembly of blood endothelial cells *Arterioscler Thromb Vasc Biol* 31(5) 1141–1150 https://doi.org/10.1161/ATVBAHA.110.218206 PMID: 21393582

48. Kolas N (2018). Regulation of Cell and Gene Therapy Products in Canada. Canadian Blood and Bone Marrow Transplant Group.

49. Lapillonne H, Kobari L, and Mazurier C, *et al* (2010). Blood cell generation from human induced pluripotent stem cells: perspectives for transfusion medicine Haematologica 95(10) 1651–1659 https://doi.org/10.3324/haematol.2010.023556 PMID: 20494935 PMCID: 2948089

50. Laura Frese, Petra E. Dijkman and Simon P. Hoerstrup (2016). Adipose Tissue-Derived Stem Cells in Regenerative Medicine. *Transfus Med Hemother. 2016 Jul; 43(4): 268–274. Published online 2016 Jul 26. doi: 10.1159/000448180*

51. Ming Li, Kequan Guo and Susumu Ikehara (2014). Stem Cell Treatment for Alzheimer's Disease. *International journal of molecular sciences. 15. 19226-19238.* 10.3390/ijms151019226.

52. Locke M, Windsor J and Dunbar PR (2009) Human adipose-derived stem cells: isolation, characterization and applications in surgery. *ANZ J Surg 79 235–244 https://doi.org/10.1111/j.1445-2197.2009.04852.x PMID: 19432707*

53. Luetzkendor Jana et al (2015). Cryopreservation does not alter main characteristics of Good Manufacturing Process–grade human multipotent mesenchymal stromal cells

including immunomodulating potential and lack of malignant transformation. *Cytotherapy. Volume V17, Issue 2, February 2015, Pages 186-198.*

54. Mahmoudifar N and Doran PM (2015). Mesenchymal Stem Cells Derived from Human Adipose Tissue (2015). *Methods Mol Biol. 2015;1340:53-64. doi: 10.1007/978-1-4939-2938-2_4.*
55. Marjorie E. Bateman et al (2018). Concise Review: Using Fat To Fight Disease: A Systematic Review Of Nonhomologous. Adipose-derived Stromal/Stem Cell Therapies. Regenerative Medicine. *Stem Cells. 2018 Sep;36(9):1311-1328*. doi: 10.1002/stem.2847. Epub 2018 Jul 16.
56. Maruyama Y (2019). Regulation of Regenerative Medicine in Japan. *Health Product Regulatory Conference. Academia*. Available on: https://www.pmda.go.jp/files/000219466.pdf (accessed on 29/05/19).
57. Meirelles Lda S, Fontes AM, Covas DT and Caplan AI (2009). Mechanisms involved in the therapeutic properties of mesenchymal stem cells. *Cytokine Growth Factor Rev. 2009 Oct-Dec;20(5-6):419-27. doi: 10.1016/j.cytogfr.2009.10.002. Epub 2009 Nov 18.*
58. Ministry of Health Malaysia (2017). Guidelines for Stem Cell Research and Therapy. *Medical Development Division,* Ministry Of Health Malaysia. Available on: https://www.crc.gov.my/wp-content/uploads/documents/MALAYSIAN%20GUIDELINES%20FOR%20STEM%20CELL%20RESEARCH%20AND%20THERAPY%202009%20.pdf (accessed on 29/05/19).

59. Minonzio Greta et al (2014). Frozen adipose-derived mesenchymal stem cells maintain high capability to grow and differentiate. *Cryobiology. 2014 Oct;69(2):211-6. doi: 10.1016/j.cryobiol.2014.07.005. Epub 2014 Jul 15.*

60. Mishra PK (2008). Bone marrow-derived mesenchymal stem cells for treatment of heart failure: is it all paracrine actions and immunomodulation? *J Cardiovasc Med (Hagerstown). 2008 Feb;9(2):122-8.* doi: 10.2459/JCM.0b013e32820588f0.

61. Na YK, Ban JJ, and Lee M (2017) Wound healing potential of adipose tissue ítem cell extract. *Biochem Biophys Res Commun 485(1) 30–34 https://doi.org/10.1016/j.bbrc.2017.01.103 PMID: 28137582.*

62. Naderi N et al (2017). The regenerative role of adipose-derived stem cells (ADSC) in plastic and reconstructive surgery. *Int Wound J. 2017 Feb;14(1):112-124. doi: 10.1111/iwj.12569. Epub 2016 Feb 1.*

63. NHS Health Research Authority and Human Tissue Authority (2018). Regulation of regenerative medicine in the UK, May 2018. Available on: https://www.hta.gov.uk/sites/default/files/migrated_files/Role_of_regulators_in_regenerative_medicine.pdf (accessed 29/05/19).

64. Nicholas Toscano, Danny Holtzclaw and Steven Victor (2011). A Prospective Pilot Study on the Clinical Application of Stromal Vascular Fraction Stem Cells in the Treatment of Miller Class I and II Gingival Recession Defects. *The Journal of Implant & Advanced Clinical Dentistry, 2011.*

65. Nofianti Chyara et al (2018). Temporary storage solution for adipose derived mesenchymal stem cells. *Stem Cell Investig. 2018; 5: 19. Published online 2018 Jun 7. doi: 10.21037/sci.2018.05.04. PMCID: PMC6044052, PMID: 30050919.*

66. Pablo Bora and Anish S. Majumdar (2017). Adipose tissue-derived stromal vascular fraction in regenerative medicine: a brief review on biology and translation. Stem Cell *Res Ther. 2017; 8: 145. Published online 2017 Jun 15. doi: 10.1186/s13287-017-0598-y.*

67. Pham Phuc. (2017). Stem Cell Therapy for Autism. Neurological Regeneration (pp.121-136). DOI: 10.1007/978-3-319-33720-3_7. *Publisher: 2365-4198 Stem Cell Therapy for Autism.*

68. Phanette et al (2012). Clinical Application of Autologous. Adipose Stem Cells. *Department of Plastic Surgery*, *University of Texas, 2012.*

69. Prockop et al (2008). Mesenchymal Stem Cells. Methods and Protocols. Methods in Molecular Biology.

70. Puissant B et al (2005). Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol. 2005 Apr;129(1):118-29.*

71. Rachel C. Nordberga and Elizabeth G. Loboa (2015). Our Fat Future: Translating Adipose Stem Cell Therapy. *Stem Cells Transl Med. 2015 Sep; 4(9): 974–979. PMCID: PMC4542878.*

72. Reza Tabatabaei Qomi and Mohsen Sheykhhasan (2017). Adipose-derived stromal cell in regenerative medicine: A review. *World J Stem Cells. Aug 26, 2017; 9(8): 107-117*. Published online Aug 26, 2017. doi: 10.4252/wjsc.v9.i8.107

73. Robert Alexander (2012). Understanding Adipose-derived Stromal Vascular Fraction (AD-SVFCS) Cell Biology and Use on the Basis of Cellular, Chemical, Structural and Paracrine Components: A Concise Review. *Journal of Prolotherapy. 2012;4:e855-e869.*

74. Rongrong Sun et al (2016). Advances in stem cell therapy for cardiovascular disease (Review). May 25, 2016. Available from: https://doi.org/10.3892/ijmm.2016.2607 (accessed 16/03/19).

75. Rosalinda Madonna , Yong-Jian Geng and Raffaele De Caterina. Adipose Tissue-Derived Stem Cells (2009). Characterization and Potential for Cardiovascular Repair. Originally published 23 Jul 2009 https://doi.org/10.1161/ATVBAHA.109.187179 *Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;29:1723–1729*.

76. Safford KM et al (2002). Neurogenic differentiation of murine and human adipose-derived stromal cells. Biochem Biophys *Res Commun. 2002 Jun 7;294(2):371-9.*

77. Sarmila Nepali et al (2018). Comparative Analysis of Human Adipose-Derived Mesenchymal. Stem Cells from Orbital and Abdominal Fat. *Hindawi Stem Cells International Volume 2018,* Article ID 3932615, 9 pages https://doi.org/10.1155/2018/3932615

78. Seo E et al (2017). Exendin-4 in combination with adipose-derived stem cells promotes angiogenesis and improves diabetic wound healing. *J Transl Med. 2017 Feb 15;15(1):35. doi: 10.1186/s12967-017-1145-4.*

79. Shaik Shahensha, Wu Xiying, Gimble Jeffrey and Devireddy Ram (2018). Effects of Decade Long Freezing Storage on Adipose Derived Stem Cells Functionality. *Scientific Reports (2018) 8:8162, DOI:10.1038/s41598-018-26546-7*

80. Shologu N et al (2018). Human Mesenchymal Stem Cell Secretome from Bone Marrow or Adipose-Derived Tissue Sources for Treatment of Hypoxia-Induced Pulmonary Epithelial Injury. *Int J Mol Sci. 2018 Sep 30;19(10).* pii: E2996. doi: 10.3390/ijms19102996.

81. Simona Neri et al (2013). Human Adipose Stromal Cells (ASC) for the Regeneration of Injured Cartilage Display Genetic Stability after In Vitro Culture Expansion. *PLoS One. 2013 Oct 28;8(10):*e77895. doi: 10.1371/journal.pone.0077895. eCollection 2013.

82. Stepien A et al (2016). Clinical Application of Autologous. Adipose Stem Cells in Patients with Multiple Sclerosis: Preliminary Results. *Mediators Inflamm. 2016;2016:5302120.* Epub 2016 Sep 28.

83. The College of American Pathologists (2019). Laboratory Accreditation Program. Available on: https://www.cap.org/laboratory-improvement/accreditation/laboratory-accreditation-program (accessed 29/05/2019).

84. Thomson JA et al (2011) Embryonic stem cell lines derived from human blastocysts. *Science. 5391(282) 1145–1147*

85. Vanesa Verónica Miana and Elio A Prieto González (2018). Adipose tissue stem cells in regenerative medicine (2018). Centre for Advanced Studies in Humanities and Health Sciences, Interamerican Open University, Buenos Aires, Arge. *ecancer 2018, 12:822 https://doi.org/10.3332/ecancer.2018.822*

86. Wang X et al (2013). Role of mesenchymal stem cells in bone regeneration and fracture repair: a review. *Int Orthop. 2013 Dec;37(12):2491-8. doi: 10.1007/s00264-013-2059-2. Epub 2013 Aug 15.*

87. Yao YZ, Deng CL and Wang B (2018). Advances in the research of influence of diabetes in biological function of adipose-derived stem cells. Zhonghua Shao Shang Za Zhi. *Sep 20;34(9):653-656. doi: 10.3760/cma.j.issn.1009-2587.2018.09.017*[Article in Chinese; Abstract available in Chinese from the publisher].

88. Yin-Di Wu et al (2019). Effects of storage culture media, temperature and duration on human adipose-derived stem cell viability for clinical use. March 2019, Volume 19 Issue 3, *Pages: 2189-2201. Published online on: January 10, 2019, https://doi.org/10.3892/mmr.2019.9842.*

89. Zipori Dov (2009). Biology of Stem Cells and the Molecular Basis of the Stem State. *Chapter 2, Multipotency and Tissue-Specific Stem Cells. Springer.*

90. Zuk PA et al (2002). Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell. 2002 Dec;13(12):4279-95.*

Appendix 1- Minimum Patient and Physician Consent/Declaration

Patient Declaration: I voluntarily request (**insert physician names**) as my physician(s), and such associated staff and technical assistants deemed necessary, to treat my condition, which has been explained to my satisfaction in non-technical language. I (**insert patient name)** know the potential benefits of this (**insert procedure name)** and have talked to my treating physician(s) before participating.

I understand clearly that Autologous Adipose Derived Stem Cell Therapy is not yet the global standard of care/considered experimental in some countries and there is No Guarantee that the procedure will succeed. Receiving experimental treatment may make me ineligible for future clinical trials or treatment options and I understand that cells from my own body are not automatically safe when used in treatments and when treatment is offered for sale, it is not the same as a clinical trial.

There is a risk of infection any time cells are removed from my body, as cells may be contaminated and may in contact with viruses, bacteria or other pathogens that could cause disease when reintroduced. Stem cells may overgrow and cause tumours. Complications may create short and long-term health problems, and/or may make your condition or symptoms more difficult to manage. I understand it is prohibited to use and/or combine embryonic, amniotic, cord blood cells in any form with ADSCs and/or for the use of ADSCs manipulation to expansion. It is also prohibited to add growth factors, hormones or enzymes to my ADSCs.

I have consented for the appropriate anesthesia to be administered to carry out the procedure. The specific risks for this (**insert procedure name)** and anesthesia have been explained to me and include (**list all risks**):

Patient Name and Signature: Date: Time:

Legal guardian of the patient

if unable of consent (name and signature) Date: Time:

Treating Physician(s) Declaration: I (**insert names)** have explained the diagnosis, prognosis, alternative options and the Autologous Adipose Derived Stem Cell Therapy procedure (**insert name of procedure and site**) to be performed to treat (**insert diagnosis**) and the pertinent contents to the patient.

I have answered all the patient's questions to the best of my knowledge and, the patient has been adequately informed of the potential benefits, risks, complications and the patient has consented to the (**insert name of procedure and site)**. I (**insert names**) have explained to the patient that this treatment is not yet the standard of care, how anesthesia will be administered and the associated risks.

I will adhere to best practice and, have ensured compliance with the health facilities written protocols for this treatment and agree to assess progress of the treatment and advise the patient accordingly to the best available evidence and clinical experience.

Physician(s) name (s) and Signature: Date: Time:

Witness Name and Signature: Date: Time:

Relationship and/or Designation: