STANDARDS OF PRACTICE FOR CELLULAR THERAPY:

COLLECTION, PROCESSING, STORAGE AND DISTRIBUTION

Foreword

The first step in the process of regulating cell-based therapeutic products in South Africa was taken in 2003, when the National Health Act (Act No.61 of 2003) was promulgated into Law. Specific regulations relating to stem cells were published by the Department of Health in 2012, marking a significant era in the regulation of cell-based therapy in the country.

Stem cell products hold a great deal of promise to treat human disease and prevent suffering as they have the potential to provide treatments for a host of debilitating diseases including diabetes, multiple sclerosis, heart disease, and spinal cord injuries. At the same time, their derivation and use raise ethical and social issues and legal concerns of interest to all. It is the potential use and abuse as well as the cost of stem cell therapy that has attracted the attention of the general population.

In response to the need for clear guidelines that would allow for responsible handling of cell-based therapeutic products, the National Department of Health in collaboration with a team of experts from around the country developed guidelines on standards of practice for cell therapy product collection, processing, storage and distribution. The aim of the guidelines is to provide minimum criteria for the safe and effective management of Cellular Therapy Product Services in South Africa. The guidelines begin by clarifying definitions, and then enumerate minimal management and technical requirements. Embedded in the guidelines are recommendations for the development of an institution's quality management system.

I am therefore proud to present the guidelines which will be a valuable tool for the Department of Health to monitor the provision of quality stem cell therapy products in the country.

Acknowledgements

The Department would like to acknowledge the following individuals who contributed to the development of the guidelines:

Authors

Professor Michael Pepper – Director: Institute for Cellular and Molecular Medicine, University of Pretoria
Dr Charlotte Ingram – Medical Director: South African National Blood Services
Dr Yvonne Holt – Medical Director: Netcells
Dr Robert Crookes – Medical Director: Cryo-Save South Africa
Ms Laurel Anderson – National SHEQ Internal Audit Manager: South African National Blood Services
Professor Melodie Slabbert – Deputy Dean, Faculty of Law, Unisa

Contributors

Ms Lineo Motopi - Medical Scientist: Trauma, Violence, Emergency Medical Services and Forensic Pathology Services

TABLE OF CONTENTS

1. BACKGROUND AND PURPOSE

The purpose of these standards is to provide minimum criteria for the safe and effective management of Cellular Therapy Product Services in South Africa.

South Africa is faced with a high disease burden which includes both communicable (infectious) and non-communicable diseases (including diseases of lifestyle and cancer), high maternal and infant mortality rates, and the consequences of injury and violence. Novel approaches are urgently needed to deal with this quadruple burden of disease. One of the most exciting and rapidly growing areas of medical research involves the use of cellular therapeutic products for the treatment of patients with a variety of diseases and for tissue repair.

Cell therapy products include but are not limited to stem cells. Although stem cell research and therapy are accelerating rapidly in many countries, they have in the past been limited in South Africa. It should however be noted that stem cell therapy has been practiced for many years, in South Africa and world-wide, in the form of hematopoietic stem cell transplantation (mainly for haematological malignancies). Clinical trials are underway globally to assess the potential therapeutic effect of cell-based products in a variety of neurological, cardiovascular and metabolic diseases. However, virtually nothing has been done to explore the great potential offered by stem cells in a variety of other diseases which are relevant to our country, including infectious diseases such as HIV and tuberculosis.

Stem cells are able to divide and differentiate into all the cells that make up the tissues of our body. From a therapeutic perspective, two types of stem cells can be defined: pluripotent and adult stem cells. At present, pluripotent cells can be obtained by two means: from embryos (called embryonic stem cells) or by reprogramming adult cells (called induced pluripotent stem (iPS) cells). Adult stem cells are either hematopoietic stem cells (HSCs) or mesenchymal stem cells (MSCs). Most other stem cell types can be classified under these broad definitions.

Given the fact that on the one hand, the number of legitimate indications for cell-based therapy are at present limited, and on the other that the general public is increasingly aware of the therapeutic potential of cell-based therapeutic products, there is an increasing and alarming emergence of purported therapies that are being applied to emotionally vulnerable patients without these therapies having been adequately tested prior to administration. Equally alarming is the apparent lack of standardization, both from a governance and technical perspective, which is required to ensure two of the primary pillars of ethical conduct, namely beneficence and non-maleficence.

The purpose of these standards is to provide a minimum number of criteria that would be required by any entity in South Africa that wishes to collect, process, store and/or distribute cell-based therapeutic products, both from a management/governance and technical perspective.

2. REFERENCES

2.1 Standards for Cellular Therapy Product Services AABB, 6th Edition available as of July2013
2.2 Standards of Practice for Blood Transfusion in South Africa, 6th Edition, 2013
2.3 ISO 9000:2005
2.4 The International Standards for Cellular Therapy Product Collection, Processing and Administration, 2012

3. DEFINITIONS

3.1 **AGREEMENT**

3.1.1 **Agreement:** a contract, order, or understanding between two or more parties.

3.1.2 **Agreement review:** systematic activities carried out by two or more parties before finalising the agreement to ensure that requirements are adequately define, free from ambiguity, documented and achievable by the supplier.

3.1.3 **Educational and promotional materials:** information made available by the cellular therapy facility to potential donors, patients and others.

3.1.4 **Informed consent:** a process of communication between a patient/donor and attending clinician/registry that results in the patient/donor authorising an agreement to undergo a specific medical intervention, after being comprehensively informed of the risks, discomforts, benefits and alternatives relating to the specific intervention.

3.1.5 **Notification:** informing relevant persons of specific facts, e.g. to suppliers if goods are received in an unacceptable condition.

3.1.6 **Obtaining materials and services:** evaluation of suppliers, qualifications of facilities providing tests or services.

3.1.7 **Physician orders:** medical therapy orders and procurement of such an order.

3.1.8 **Registry requests:** requests made by the SABMR based on Physician's orders.

3.2 **DEVIATIONS AND NON-CONFORMING PRODUCTS OR SERVICES**

3.2.1 **Adverse event:** any unintended or unfavourable, sign, symptom, abnormality or condition temporally associated with an intervention that may or may not have a causal relationship with the intervention, medical treatment or procedure.

3.2.2 **Adverse reaction:** (an adverse reaction is a type of adverse event). A noxious and unintended response to the collection or infusion of any cellular therapy product for which there is a reasonable possibility that the cellular therapy intervention caused the response.

3.2.3 **Corrective action:** the action taken to eliminate the cause of a detected non-conformity or other undesirable situation to minimise its reoccurrence.

3.2.4 **Deviations:** departure from an agreed-upon course, design mean or method.

3.2.5 **Non-conformance:** failure to comply with specified requirements.

3.2.6 **Non-conforming product or service:** a product or service that does not satisfy one or more specified requirement.

3.2.7 **Preventive action:** an activity performed to eliminate the potential for non-conformance or other undesirable situations.

3.2.8 **Root cause analysis:** a technique used to identify the conditions that initiate the occurrence of an undesired activity or state.

3.3 **DOCUMENTS AND RECORDS**

3.3.1 **Documentation:** all written documents that provide consistent information to ensure operational and from a quality perspective that the requirements of these standards are met and maintained.

3.3.2 **Document control:** the control of the issue, use and review of authorised documents within the Quality Management System.

3.3.3 **Electronic records:** information captured through electronic means and which may or may not have a paper record to back it up.

3.3.4 **Procedure:** a description of how an activity is to be performed.

3.3.5 **Quality records:** information captured in writing or electronically that provides objective evidence of activities that have been performed or results that have been achieved.

3.4 **EQUIPMENT**

3.4.1 **Control of equipment:** the control, maintenance and monitoring of critical equipment.

3.4.2 **Equipment:** a durable item, instrument or device used in a process or procedure.

3.5 **INTERNAL AND EXTERNAL ASSESSMENTS**

3.5.1 **External assessment:** an objective assessment of a facilities operation and performance by an external agency or personnel.

3.5.2 **Internal assessment:** a systematic and independent examination of the quality management system and related activities by an internal assessment team to determine whether activities comply with planned arrangements, are implemented effectively and are appropriate to achieve defined objectives.

i. **Compliance assessments:** evaluation of the system, its implementation and its effectiveness in ensuring products and services meet specified requirements.
ii. **System assessments:** evaluation of documentation and procedures.
iii. **Vendor assessments:** evaluation of the effectiveness of the products or services procured.

3.5.3 **Proficiency testing**: the structured evaluation of laboratory methods that assesses the performance of the test system.

3.6 **ORGANISATION** (Facility)

3.6.1 **Emergency operation plans:** plans in case of disaster and other emergencies.

3.6.2 **Environmental monitoring:** policies, process and procedures used for monitoring any or all of the following: temperature, humidity, particulates and microbial contamination in a specific area. Where appropriate, the program must include sampling sites, frequency of sampling and investigative and corrective actions that should be followed when specified limits are exceeded.

3.6.3 **Facility:** a location where any activities relating to cellular therapy products are performed.

3.6.4 **Good laboratory practice:** ensure that laboratory functions are carried out in accordance with regulatory requirements.

3.6.5 **Legal custodian:** a person legally responsible for the donor until the donor's age of majority

3.6.6 **Management:** senior personnel appointed to supervise and manage designated departments of a Cellular Therapy Service.

3.6.7 **Quality assurance:** planned and systematic activities defined in a quality management system within facility, to provide adequate confidence that Cellular Therapy services meet relevant specifications and quality requirements.

3.6.8 **Quality management system:** a system including the establishment of a quality policy, quality objectives and the overseeing of all activities required to maintain the desired level of excellence and implementation of continual improvement.

3.6.9 **Quality objectives:** defined objectives and commitments pertaining to key elements of quality, such as fitness for use, performance, safety and dependability.

3.6.10 **Quality policy:** the management of a facility must define and document its quality policy. This policy must be consistent with other policies, within the organisation. Management must take all necessary measures to ensure that its quality policy is understood, implemented and reviewed at all levels of the organisation.

3.7 **PROCESS CONTROL**

3.7.1 **Accuracy:** the degree to which the measured value agrees with the true value of the measurement.

3.7.2 **Allogeneic:** derived from separate individuals of the same species. Genetically dissimilar within the same species.

3.7.3 **Aseptic technique:** a practice designed to reduce the risk of microbial contamination of products, reagents, specimens or persons.

3.7.4 **Autologous:** a cellular component derived or transferred from the same individual's body.

3.7.5 **Biological product deviation:** A deviation from applicable regulations, standards or established specifications that:

i. That relate to the prevention of communicable disease transmission or cellular therapy product contamination;

ii. An unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to cellular therapy product contamination.

3.7.6 **Calibrate:** to set or align measurement equipment against a known standard.

3.7.7 **Calibration:** a set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument system or values represented by a material measure and the corresponding known values of a reference standard. Procedure that confirms under defined conditions, the relationship between values obtained from an instrument or system with those obtained using an appropriated certified standard. It may also include the adjustment activity.

3.7.8 **Cellular therapy:** the administration of cells with the intent of providing effector cells in the treatment of disease or support of other therapy.

3.7.9 **Cellular therapy product:** somatic cell-based products that are procured from a donor and intended for manipulation and/or administration.

3.7.10 **Change control:** a systematic approach to managing all changes made to a product or system.

3.7.11 **Clinical outcomes**: clinical data and outcomes of patients to be reviewed as part of quality program.

3.7.12 **Competency:** the ability to perform a specific procedure or task according to instruction and to produce consistent results with a specified accuracy. To be certified as qualified to the appropriate task.

3.7.13 **Continuous improvement:** the actions taken to enhance the features and characteristics of products and or services and to increase the effectiveness and efficiency of the processes used to produce and deliver them.

3.7.14 **Continuous monitoring:** a mechanism that allows for surveillance of a process or system intended to ensure proper operation the detection of control exceptions.

3.7.15 **Cord blood:** the whole blood, including haematopoietic progenitor cells collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.

3.7.16 **Cryopreservation:** the process of low-temperature freezing and storage of cellular therapy products in order to preserve cells that, after thawing, retain measure of their pre-freeze viability and function.

3.7.17 **Cryopreserved product:** a cellular product that has been stored frozen, either in liquid nitrogen or in a mechanical deep freeze at below -80 degrees centigrade.

3.7.18 **Donor:** A person who is the source of cells or tissue for a cellular therapy product.

3.7.19 **Donor eligibility:** evaluation of cellular therapy donors for risk factors and clinical evidence of relevant infectious disease agents or diseases for the purpose of preventing the introduction, transmission and spread of infectious diseases. The donor/s must agree to provide information related to the biological family medical and genetic history.

3.7.20 **Donor evaluation:** how donor evaluation should be performed (history, tests), informed consent.

3.7.21 **Donor suitability:** evaluation of cellular therapy donors for risks related to the donation process.

3.7.22 **Engraftment:** The reconstitution of recipient haematopoiesis with cells from the bone marrow or cord blood.

3.7.23 **Evaluation to make a product available for distribution:** definition of inspections and tests required for product distribution.

3.7.24 **Expansion:** Growth of one or more cell populations in an in vitro culture system.

3.7.25 **Fresh product:** A cellular product that is used within a defined period after minimum manipulation.

3.7.26 **Gene insertion:** The introduction of one or more exogenous genes into one or more cell populations.

3.7.27 **Haematopoietic progenitor cells (HPC's):** Self-renewing and or multi-potent stem cells capable of maturation into any of the haematopoietic lineages, lineage-restricted

pluripotent progenitor cells and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood or other tissue source).

3.7.28 **Haematopoietic progenitor cell therapy:** The infusion of a HPC product with the intent of providing effector functions in the treatment of disease or in support of other therapy.

3.7.29 **Haematopoietic stem cell therapy:** The infusion of a HPC product with the intent of providing effector functions in the treatment of disease or in support of other therapy.

3.7.30 **Human cells, tissues or other cellular components (HCT):** Human cells or tissues intended for implantation, transplantation, infusion or transfer into a human recipient.

3.7.31 **Ineligible donor:** a designation applied to a donor who is not acceptable as a donor for a specific reason, e.g. whose product may be at risk of transmitting an infectious disease as detected by testing and/or donor screening history.

3.7.32 **Inspection and testing:** receipt of incoming cells, tissue, organs. Records of initial testing that is required.

3.7.33 **Label:** an inscription affixed to a product for identification.

3.7.34 **Labelling:** information that is required or selected to accompany a cellular therapy product.

3.7.35 **Maintenance:** preventative maintenance is the care and servicing of equipment and facilities. It is the systematic inspection, detection and correction of incipient failures either before they occur or before the development into major defects.

3.7.36 **Manipulation:** An ex vivo procedure that functionally alters HPC.

3.7.37 **Materials management:** receipt, how they are used, records of materials (expiry dates, serial numbers, and lot numbers).

3.7.38 **Mesenchymal stem cells:** (MSC's) are multipotent stromal cells that can differentiate into a variety of cell types, including: osteoblasts (bone cells), chondrocytes (cartilage cells), and adipocytes (fat cells).

3.7.39 **Microbial:** Involving infectious agents including bacterial and fungal organisms.

3.7.40 **Minimally manipulated:** Processing that does not alter the relevant biological characteristics of cells or tissues.

3.7.41 **Negative selection:** The manipulation of a cellular therapy product such that a specific ell population/s is depleted.

3.7.42 **Peripheral blood stem cells (PBSC's):** Self-renewing or multi-potent stem cells derived from peripheral blood, capable of maturation into any of the haematopoietic lineages, lineage-restricted pluripotent progenitor cells and/or committed progenitor cells.

3.7.43 **Physician:** Medical specialist registered with the HPCSA.

3.7.44 **Positive selection:** The manipulation of a cellular therapy product such that a specific cell population/s is enriched.

3.7.45 **Potency:** The therapeutic activity of a product as indicated by appropriate laboratory tests adequately developed and controlled clinical data.

3.7.46 **Precision:** closeness of agreement between results of measurement obtained under stipulated conditions.

3.7.47 **Process:** a set of related tasks and activities that accomplishes a work goal.

3.7.48 **Process control:** designing and validating processes and procedures that affect the quality of cellular therapy products and services in order to produce predicable outputs.

3.7.49 **Procurement:** the act of obtaining a cellular therapy product(s) from a donor by facility approved methods.

3.7.50 **Procurement endpoints:** the product characteristics that meet the procurement goal or that can safely be obtained.

3.7.51 **Product issue:** obtaining a medical order, list of requirements recorded for distribution e.g. label inspection, correlation with donor and recipient details, records of required tests.

3.7.52 **Proficiency testing:** the evaluation of participant performance against pre-established criteria by means of inter-laboratory comparisons.

3.7.53 **Quality control:** *the operational techniques and activities that are used to fulfil requirements for quality*.

3.7.54 **Sepsis:** systemic inflammatory response due to an infectious agent and accompanied by characteristic clinical and laboratory findings.

3.7.55 **Stem cell donor:** A person who is the source of cells or tissue for a cellular therapy product.

3.7.56 **Storage and preservation:** specifications on storage equipment required for cryopreservation. Control of stored inventory. Storage required at administration site after issue.

3.7.57 **Syngeneic product:** Cellular therapy product collected from a donor and intended for infusion into a genetically identical twin.

3.7.58 **Traceability:** the ability to trace the history, application or location of an item, activity or result by means of recorded identification.

3.7.59 **Transport and shipping:** to processing facility.

3.7.60 **Transplant physician:** the physician responsible for the recipient to whom the haematopoietic stem cells will be infused.

3.7.61 **Validation:** the demonstration through objective evidence that the requirements for a particular application or intended use have been met.

3.7.62 **Verification:** the process of evaluating objective evidence that a product, service or system meets specifications and that if fulfils its intended purpose.

3.7.63 **Viability:** the demonstrated capability of living; indicating (either in-vivo or in-vitro ability to perform physiologic functions.

3.8 **PROCESS IMPROVEMENT**

3.8.1 **Conformance:** fulfilment of requirements.

3.8.2 **Corrective and preventative action plans:** plans to deal with non-conformances.

3.9 **RESOURCES**

3.9.1 **Competence:** ability of an individual to perform a specific task according to procedures evaluated on an on-going basis.

3.9.2 **Designee:** an individual with appropriate experience or expertise who is given the authority to assume a specific responsibility.

3.9.3 **Financial:** money that is available for an organisation to spend.

3.9.4 **Human resources:** the set of individuals who make up the workforce of an organisation.

3.9.5 **Management responsibility:** the responsibility for and commitment to a quality management system belongs to the highest level of management. Quality management encompasses all activities of the overall management function that determines the quality policy, objectives and responsibilities and implementation by means of quality planning, quality control, quality assurance and quality improvement within the quality management system.

3.9.6 **Resources:** the financial or productive factor required to accomplish an activity. Three basic resources are land labour and capital; other resources include energy, entrepreneurship, information, expertise, management and time.

3.10 **SAFETY AND FACILITIES**

3.10.1 **Collection facility:** the facility where haematopoietic stem cells are collected from donors.

3.10.2 **Facilities and environmental controls:** monitoring requirements of laboratory and storage facility.

3.10.3 **Safety:** health and safety requirements of such a facility.

3.10.4 **Transplant facility:** the facility where the recipient is managed and where the haematopoietic stem cells are infused.

4. MANAGEMENT REQUIREMENTS

4.1 ORGANISATION AND STRUCTURE

4.1.1 The responsibility, authority and relationship of personnel performing, verifying or managing activities defined in this standard must be defined.

4.1.2 The facility must have arrangements to ensure that commercial, financial and other pressures do not adversely affect the quality of the work of its personnel.

4.1.3 The facility must be organised in such a way that confidence in its independence of judgement and integrity is maintained at all times.

4.1.4 **Executive Management:** the facility must define executive management. The executive management must have the responsibility and authority for the facility's operations, for appointing a quality representative, for performing management reviews and for compliance with these standards and applicable laws and regulations.

4.1.5 **Facility/Laboratory Director:** the facility should be under the direction of a designated person/s with a degree in the health or natural sciences, preferably but not necessarily an MBChB or a PhD, qualified by training and/or experience and relevant continuous education for the specific cellular therapy services. The facility/ laboratory director must be responsible and accountable for ensuring that all operations are carried out properly and competently as required by the relevant laws and regulations. When the Laboratory/Facility Director delegates these responsibilities to a designee, the laboratory director must retain ultimate responsibility.

4.1.6 **Medical Director:** the facility must have a medical director who is registered with the Health Professions Council (HPCSA) and qualified by training and or experience in Cell Therapy Services. The medical director must have the responsibility and the authority for all medical matters related to the provision of cellular therapy products and related services. The medical director may delegate these responsibilities to another qualified medical professional; however, the medical director must retain ultimate responsibility for the delegated duties. Exceptions to procedures warranted by clinical situations must require justification and pre-approval by the medical director on a case-by-case basis. This deviation must be documented.

4.1.7 **Quality Representative/Manager:** a designated individual must be appointed with overall responsibility for the quality within the facility. This individual must be responsible for establishing, implementing and maintaining of the quality management system. The Quality Manager must report directly to Executive Management or to another designated individual who has no direct managerial or supervisory role in the collection, processing, testing or distribution of Stem Cell products.

4.1.8 **Technical Manager:** a designated individual who has overall responsibility for the technical operations. The technical manager must report directly to executive management or to another designated individual who has no direct managerial or supervisory role in technical operations.

4.1.9 **Technical personnel:** training and CPD and periodic competency testing.

4.1.10 Nominate deputies must be defined in the case of absence of the technical manager and the quality manager.

4.2 RESOURCES

The facility must identify and provide adequate staffing, materials, equipment and facility infrastructure to perform, verify and manage all activities covered by these Standards.

4.2.1 **Financial resources**: the facility must identify financial resource requirements adequate to perform, verify and manage its activities. The facility must develop a budget to ensure its on-going operation. The facility must undergo annual financial audits.

4.2.2 **Human resources:** the facility must have sufficient, trained, qualified and competent managerial and technical personnel to carry out their duties.

4.2.3 **Job Qualifications**: Job descriptions must outline key responsibilities and duties to be performed and identify appropriate qualifications for each job position on the basis of education, training and/or experience.

4.2.4 **Training**: the facility must have a training policy and documented program to ensure all personnel are trained and competent to perform their assigned activities. The facility must have a system in place to identify training needs of staff. The qualifications of the trainers must be defined.

4.2.5 **Competence**: the facility must have a system in place to evaluate the competence of defined tasks and activities for all staff.

4.2.6 **Training Records**: records must be kept of staff training and competency evaluations.

4.2.7 **Personnel identification:** records must be maintained of names, signatures, initials or other means of identification and inclusive dates of employment for all members of staff.

4.2.8 **Continuous education:** requirements for continuous education must be met by all relevant employees.

4.3 QUALITY MANAGEMENT SYSTEM

4.3.1 The facility must design, implement and maintain a Quality Management System to ensure that cellular therapy products and services conform to specified requirements.

4.3.2 The facility must maintain a quality manual that defines how the elements of this standard apply or have been implemented.

4.3.3 The quality manual must describe the quality management system and the structure of the documentation used in the quality management system. The quality manual must include or make reference to the supporting procedures including technical procedures. It must outline the structure of the documentation in the quality management system. The roles and responsibilities of technical management and the quality manager, including their responsibilities for ensuring compliance with this standard must be defined in the quality manual.

4.3.4 **Management review:** management must review and evaluate the quality system at planned intervals and take action to ensure continued suitability, adequacy and effectiveness.

4.3.5 **Emergency operation plans:** the facility must have emergency operation plans to respond to the effects of disasters and other emergencies.

4.3.6 **Policies, processes and procedures:** the facility must develop and implement quality and operational policies, process and procedures to ensure the requirements of this standard are met.

4.3.7 The quality system must be communicated to all personnel so that they understand their role in ensuring quality. Personnel must familiarise themselves with the quality system.

4.3.8 The facility must implement internal quality control and participate in organised inter-laboratory comparisons such as external quality assessment schemes.

4.4 MANAGEMENT REVIEW

4.4.1 The facility management must review the quality management system at defined intervals to ensure its continued suitability and effectiveness and to introduce any changes or improvements.

4.4.2 The results of the review must be incorporated into a plan that includes goals, objectives and action plans.

4.4.3 The review must take into account, but not be limited to:

i. Follow-up of previous management reviews
ii. Status of corrective actions taken and required preventive action
iii. Reports from managerial and supervisory personnel
iv. The outcome of recent internal assessments
v. The outcome of external assessments
vi. The outcome of external quality assessments and other forms of inter-laboratory comparisons
vii. Any changes in the volume and type of work undertaken

viii. Feedback, including complaints and other relevant factors from clinicians, donors, patients and other parties
ix. Quality indicators for monitoring the facilities contribution to patient/donor care
x. Non-conformances
xi. Results of continuous improvement processes
xii. Evaluation of suppliers
xiii. Suitability of policies, processes and procedures
xiv. Corrective and preventive actions (trend analysis)
xv. Other relevant factors such as resources and staff training

4.5 **DOCUMENT CONTROL**

4.5.1 The facility must establish, implement and maintain policies, processes and procedure to control all documents and information (from internal and external sources) that relate to the requirements of this standard.

4.5.2 The document control system must address:
i. The documents unique identification
ii. Title
iii. Edition or current revision date, or revision number
iv. Number of pages
v. Authority for issue

4.5.3 The policies, processes and procedures must be in a standardised format.

4.5.4 The documents must be uniquely identified, be current and dated to prevent the use of invalid or obsolete documents.

4.5.5 The documents must be reviewed and approved by authorised personnel prior to use.

4.5.6 Invalid or obsolete documents must be removed from all points of use, or otherwise identified.

4.5.7 Changes to procedures must be approved by authorised personnel responsible for making the change the nature of the change must be documented.

4.5.8 If the facilities document control system allows for the amendment of documents by hand pending the re-issue of documents, the procedure and authorities for such amendments must be defined, amendments must be clearly marked, initialled and dated and a revised and a revised document to be issued as soon as is practicable.

4.5.9 The document control system must describe how changes to documents maintained in a computerised system are to be made and controlled.

4.5.10 The document control system must ensure that all appropriate documents are legible and readily accessible to personnel who rely on them to perform activities. Methods of copying/archiving must be defined.

4.5.11 The facility must maintain an index list of all current documents.

4.6 **RECORDS**

4.6.1 The facility must establish and maintain policies, process and procedures for:
i. Record identification
ii. Procurement
iii. Indexing
iv. Accessing
v. Filing
vi. Storage
vii. Maintenance and
viii. Disposition of records

4.6.2 Records must be legible, complete, retrievable and protected from damage.

4.6.3 The storage of records must be designed to prevent unauthorised access, copying, modification or destruction and ensure confidentially of records will be maintained.

4.6.4 The storage of records must ensure that there is traceability from source to final disposition, the environment is suitable and in a manner that prevents mix-ups, damage, deterioration and loss.

4.6.5 Records must be maintained to demonstrate products or services conform to specific requirements and that the quality system is effectively operated. Pertinent records from suppliers must be an element of this information.

4.6.6 The facility must establish and maintain appropriate processes for changes made to records. The date and identify of the person making the change must be recorded. Record changes must not obscure previously recorded information.

4.6.7 The records must identify the work performed, the person performing the activity and when it was performed.

4.6.8 Before destruction of the original records, copies of the records must be verified as containing the original content and must be legible, complete and accessible.

4.6.9 The facility must have policies and procedures that ensure the confidentiality of donors, employee and patient records.

4.6.10 Records must be reviewed for accuracy, completeness and compliance with relevant standards, laws and regulations.

4.6.11 The facility must have procedures to support the management of computer systems.

4.6.12 There must be a system in place for routine backup of all critical data and the backup data must be stored in an off- site location. The backup data must be protected from unauthorised access, damage, unintended destruction, loss or modification.

4.6.13 The facility must have a procedure in place to ensure electronic data is retrievable and usable and must be tested periodically.

4.6.14 Data integrity must be maintained.

4.6.15 Records to be maintained indefinitely:

i. Quality System Records

1	Responsibility, authority and relationship of personal who perform, verify or manage work
2	The established quality system
3	Policies, process and procedures pertinent to the quality system
4	The medical director's review and approval of all medical policies, process and procedures
5	The review and approval of all technical policies, process and procedures
6	Quarterly and annual reports by quality manager to executive management
7	Management Review reports
8	Operation and emergency plans to respond to the effects of disasters and other emergencies
9	Job Descriptions and job qualifications for each position
10	Records of names, signatures, initials or identification codes and inclusive dates of employment for personnel who perform activities that affect product or service quality
11	Identification of training needs and provisions of training for all personnel who perform activities that affect product or service quality
12	Identification of qualifications required for all trainers
13	Evaluation of competence
14	Continuous Professional Develop of relevant employees
15	Control of equipment, including selection, qualification, unique identification, calibration, investigation of equipment fount to be out of specification and assessment of the validity of results obtained and of the conformance of products provided using the equipment
16	Implementation and modification of software, hardware or databases
17	Review of agreements before acceptance
18	Clinician's orders for medical therapy, procurement, processing, preservation,

	storage and administration
19	Agreements with administering facility for creation and retention of records of administration and outcomes
20	Agreement between processing/issuing facility and the administering facility or registry for access or relevant procedures and records of administration or adverse events
21	Claims in educational and promotional materials
22	Informed consent
23	Evaluation, selection and monitoring of suppliers
24	Qualification of facilities providing tests or services
25	Notification of shipping facility and manufacturer when materials are received in an unacceptable condition
26	Clinical outcome data
27	Validation and implementation of methods, both established and novel
28	Change control
29	Quality Control
30	Qualification of all materials used in the processing of cellular therapy products
31	Qualification and monitoring of equipment, materials and methods used in cleaning and sterilisation of non-single-use materials
32	Use of and identification of critical materials that come into contact with the cellular therapy product
33	Package inserts, certificates of analysis or any manufacture's documentation, including recall or defect notices, advisories, etc. for all materials used
34	Qualification of shipping containers and periodic requalification
35	Inspection and testing activities
36	Monitoring of temperature and/or liquid nitrogen levels in storage devices
37	Stability program for each type of cellular therapy product
38	Disposition of products with no identified recipient due to death or no further need
39	Document control, including review and approval of all documents before use
40	Review and approval of changes to documents
41	List of all active policies, processes, procedures, labels and forms
42	Annual review of each policy, process or procedure
43	Archiving of obsolete documents
44	Record of change
45	Result of each action performed and the final interpretation
46	Before the destruction of the original records, copies of records must be verified as containing the original content and must be legible, complete and accessible
47	Review of records for accuracy, completeness and compliance with applicable, standards, laws and regulations
48	Computer system records
49	Capture, investigation, assessment and reporting of failures to meet internal or external requirements
50	Identification, documentation, evaluation, segregation and disposition of non-conforming materials and products
51	Authorised release of non-conforming products
52	Detection, reporting and evaluation of administration-related recipient adverse reactions
53	Results of internal assessments
54	Participation in external assessment program
55	Reporting of assessment results to executive management; corrective and preventive actions taken in response to the results of the assessments

56	Participation in a proficiency testing program
57	Environmental monitoring

ii. Donor Eligibility/Management Issues

1	Determination of donor eligibility and verification of acceptable procurement criteria
2	Infectious disease testing of donors
3	Donor testing in conformance with reference standards
4	Review of donor screening and infectious disease testing records
5	Communication of abnormal results on the medical history screening or testing that may affect the recipient's health
6	Ineligible donors
7	Final approval and documentation by the donor's clinician that the donor is able to proceed with the donation
8	For apheresis and marrow donors, a complete blood count, including platelet count obtained within 24 hours before each procurement procedure
9	Central venous access device placement by qualified individual
10	Evaluation of allogeneic and autologous donors for the risk of haemoglobinopathy before the administration of a mobilising agent
11	Confirmation of donor identity, at the time of procurement by two identifiers
12	Identification numbers and expiration dates of lot numbers of disposable and additives used in the procurement process
13	The complete procurement record and the review of the procurement record

iii. Unit/Recipient

1	International shipment of cellular therapy products
2	Inspection of incoming materials that come into contact the cellular therapy product or that directly affects the quality of the product
3	Identification of materials used on an emergency basis
4	Inspection of in-house regents
5	Review of aseptic methods
6	Unique identification and traceability of cellular therapy products and samples from source to final disposition
7	Labelling controls
8	Verification of product packaging and labelling
9	Transport of products
10	Monitoring of temperature for non-cryopreserved products
11	Continuous monitoring of temperature for cryopreserved products
12	Product acceptance and shipment temperature upon receipt
13	Inspection of incoming cells, tissues and organs
14	Inspection and testing of products during processing
15	Complete processing record; verification that acceptable values or ranges for defined critical characteristics for each product was obtained
16	Procedures used to manage red cell antigen incompatibility
17	Product-specific specifications and acceptable storage conditions; monitoring of product stability during storage
18	Investigation and resolution when alarms on storage devices are activated
19	Segment identification by two individuals
20	Complete cryopreservation records
21	Review of donation criteria, final processing criteria and final product specified requirements
22	Request for distribution

23	Product issue
24	Review of criteria for issue
25	Complete administration record and recipient records
26	Confirmation of identity of the product the intended recipient, using at least two identifiers
27	Identification of adverse events occurring during the infusion of final cellular therapy products and communication to the issuing facility
28	Notification by patient care service to issuing or processing facility of adverse events

4.7 INTERNAL ASSESSMENTS

4.7.1 The facility must perform internal assessments to verify that its operations comply with specified requirements.

4.7.2 The facility must establish, implement and maintain a documented assessment program for scheduling, conducting, documenting, reporting and reviewing internal assessments.

4.7.3 The internal assessment must be performed by trained and competent personnel, who are, wherever possible, independent of those activities being assessed.

4.7.4 When the assessment findings cast doubt on the correctness or validity of the activities being performed, the facility must take immediate corrective action and must notify the affected parties in writing.

4.7.5 Internal assessment results must be reviewed by personnel responsible for the area assessed, evaluated to determine the need for corrective and preventive action, communicated to appropriate staff and reported to executive management.

4.7.6 Additional or unscheduled internal assessment must be performed where the identification of non-conforming activities or departures from authorised procedures cast doubt on the compliance of activities being carried out by the facility. The facility must ensure that the appropriate areas of concern are audited as soon as possible.

4.8 NON-CONFORMANCES, CORRECTIVE AND PREVENTIVE ACTIONS

4.8.1 The facility must have a procedure to detect, capture, investigate, assess, monitor and report deviations from accepted policies, process, procedures and acceptable standards or criteria.

i. The deviation must be reported as soon as it happens
ii. Deviations having the potential to affect the safety, purity or potency of a product; donor safety; employee safety or the safety of a patient, must be evaluated by an individual qualified to approve the release of the product. This approval must be given by the medical director, the laboratory director and/or the patient's doctor, depending on the circumstances.

4.8.2 **Corrective action**: the facility must have procedures for corrective action of non-conformances, complaints, work place accidents and incidents and must include the following:

i. A description of the non-conformance
ii. Personnel responsible for the resolution of the non-conformance
iii. Investigation of the root cause
iv. The medical significance of the non-conformance considered and where appropriate, the relevant parties informed
v. Determination of the corrective action
vi. Implementation of the corrective action
vii. Monitor the effectiveness of the corrective action
viii. Review of non-conformances to detect trends

4.8.3 **Preventive action:** the facility must have systems in place to identify areas of improvements and potential sources of non-conformities, either technical or concerning the quality system. Where preventive actions are required, action plans must be

developed, implemented and monitored to reduce the likelihood of the occurrence of such non-conformances and to take advantage of the opportunity for improvement.

4.8.4 **Customer notification:** the facility must report to the customer as soon as possible, any cellular therapy products lost, damaged or otherwise unsuitable for use or any released products or delivered services determined to be non-conforming.

4.8.5 The facility must establish and maintain policies, process and procedures to prevent the unintended use or release of non-conforming material, segregation and disposal.

4.8.6 The facility must define the responsibility for the review and authority for the disposition of non-conforming products.

4.9 AGREEMENTS

4.9.1 The facility must establish, implement and maintain policies, process and procedures for developing, approving and reviewing agreements.

4.9.2 Prior to the acceptance of a verbal or written agreement, the agreement must be reviewed by the facility to ensure:

i. The customer's requirements are adequately defined, documented and understood
ii. Any differences between the agreement requirements and the facilities services and products offered under the agreement must be resolved
iii. The facility has the capability and resources to meet the agreement requirements
iv. The facility must define how changes to agreements are made and communicated to affected parties

4.9.3 Records of reviews, including any significant changes and pertinent discussions must be maintained.

4.9.4 The review must include work referred to a subcontractor.

4.9.5 Clients must be informed of any deviation from the agreement.

4.9.6 If an agreement needs to be amended after acceptance, the same agreement review process must be repeated and any amendments must be communicated to all affected parties.

4.9.7 Any medical therapy must be ordered by a medical clinician. The orders must contain sufficient information for positive identification of the patient.

4.9.8 Orders for cellular therapy product administration must uniquely identify the patient and type of cellular therapy product ordered and must be obtained before the product is released for administration.

4.9.9 When cellular therapy products are transferred from the control of one facility to another, there must be an agreement to address the following:

i. **Providing instructions:** instructions for the receipt, handling and administration of cellular therapy product(s) and for the reporting of adverse events to the issuing facility and other parties
ii. **Records:** the responsibility of each facility involved in the procurement, processing, storage or distribution of a cellular therapy product to provide a copy of all the relevant records to another upon request

4.9.10 **Informed consent:** the informed consent documents must be reviewed and approved by the medical director.

4.9.11 **Education and promotional material:** the facility must maintain records justifying claims made in its educational and promotional material provided to potential donors, recipients and medical professions. The therapeutic and scientific claims must be reviewed and approved by the medical director.

4.10 INFORMED CONSENT

4.10.1 The informed consent must include a comprehensive explanation, in understandable terms to the consenter(s), of any applicable benefits, risks, discomforts and alternatives relating to the collection, storage, processing and distribution of the cell therapy products. Matters relating to traceability, data protection and confidentiality should also

be addressed. In addition to conforming to relevant laws and regulations, informed consent should, amongst others, refer to the following:

i. A description of the participant
ii. The consenter(s) must acknowledge in writing that he or she has received information concerning the benefits, risks, discomforts and alternative cellular therapy donation methods, that he or she has had an opportunity to have access to donor advocacy services and that he or she has been given the opportunity to ask questions and had those questions answered satisfactorily
iii. The informed consent requirements and regulations that apply to donors who are non-competent persons or persons who may temporarily lack decisional capacity must be met
iv. The consenter(s) must have the opportunity to deny or withdraw consent to the procurement procedures without affecting his or her access to medical care
v. Where relevant, an explanation of the application of the anonymity principle in the case of altruistic donation should be provided
vi. Relevant data protection laws and regulations aimed at protecting the confidentiality of, access to and the processing of personal information relating to the consenter(s).

4.10.2 **Additional informed consent:** additional informed consent requirements relevant to cord blood consenters (allogeneic and autologous) are the following:

i. Informed consent for procurement must be obtained before the mother is in active labour
ii. Consent for banking must be obtained before or within 48 hours after procurement
iii. The consenter(s) must agree to provide information related to the medical and genetic history of the biological family of the donor, where possible
iv. The length and terms of storage, the possible transfer to another facility and the disposition, including discard must be explained.

4.11 EXTERNAL SERVICES AND SUPPLIES

4.11.1 The facility must have policies, process and procedures to ensure that the qualification, receipt, handling, storage and utilisation of all materials used in the processing of cellular therapy products, conform to specified internal requirements. Critical materials must be identified and traceable.

4.11.2 The facility must receive, inspect and test all incoming materials that come into contact with the cellular therapy product or that directly affect the quality of a cellular therapy product, prior to acceptance or use.

4.11.3 Records of the following to be maintained:

i. Identification of the material
ii. Name of the manufacturer
iii. Lot number
iv. Date of receipt
v. Date of manufacture and/or expiration date
vi. Results of visual inspection upon receipt (if applicable)
vii. Indication of acceptance or rejection
viii. Certificate of analysis or manufacturer's insert (if applicable)
ix. Quantity
x. Manufacturer's instructions, including recall or defect notices, advisories and other communications related to material usage

4.11.4 Materials must be stored according to manufacturer's instructions.

4.11.5 The facility must maintain an inventory management system.

4.11.6 Purchasing documents for items affecting the quality of cellular therapy products must contain data describing the services and supplies ordered and these documents must be reviewed and approved for the technical content prior to release

4.11.7 Reagents prepared by the facility must be appropriately labelled and standardised to meet or exceed specifications. Results of tests performed on reagents must be documented.

4.11.8 The facility must have a procedure in place for the selection of services and supplies that it uses and that affect the quality of the cellular therapy product. The facility must evaluate suppliers of critical supplies and services which affect the cellular therapy products. Records of these evaluations must be maintained.

4.11.9 The facility must maintain a list of approved suppliers for critical items and the list must be reviewed at defined intervals.

4.11.10 When material is to be used in an emergency (prior to inspection), the material must be identified to permit recall and quarantine of associated products.

4.11.11 Materials that come into contact with the cellular therapy product must be sterile and of appropriate grade for intended use.

4.12 SUBCONTRACTING

4.12.1 When the facility subcontracts work, the facility must provide evidence that the subcontractors' experience and technical competence comply with appropriate standards.

4.12.2 The facility must evaluate and select sub-contractors on the basis of their ability to meet specific technical and quality assurance requirements.

4.12.3 The facility must maintain a register of all subcontractors, including the scope of subcontracting, records of the competence assessments and review the records of approved sub-contractors.

4.12.4 The facility must maintain up to date contracts and agreements with sub-contractors.

4.13 MANAGEMENT OF COMPLAINTS

4.13.1 The facility must have a policy and procedure in place for the resolution of complaints or any other feedback received.

4.13.2 Records must be maintained of all complaints, investigations and corrective actions taken by the facility.

4.14 CONTINUOUS IMPROVEMENTS

4.14.1 The facility must continuously improve the effectiveness of its quality management system in order to identify any potential sources of nonconformity or other opportunities for improvement. Action plans for improvement must be developed, documented and implemented.

5. TECHNICAL REQUIREMENTS

5.1 FACILITY/ORGANISATION (CELLULAR THERAPY PRODUCT COLLECTION)

5.1.1 Appropriate designated areas for collection of cellular therapy products, for product collected and for storage of supplies and equipment must be established.

5.1.2 The facility must be structured to prevent improper labelling, mix-ups, contamination, or cross-contamination of cellular therapy products.

5.1.3 Suitable space for confidential donor examination and evaluation must be established.

5.1.4 Donor/Patient Records:

i. Facility records to be maintained indefinitely:
   - Information sufficient to identify all facilities involved in:
     - Providing donor selection information, component collection, processing and/or testing
     - Providing recipient selection information, compatibility testing, record-keeping, treatment for disease and/or infusion of PBSC's.

ii. General records to be maintained indefinitely:

- Names, signatures and initials and inclusive dates of employment of those authorised to sign or initial or review reports and records.
- Technical Personnel:
  - Employee Qualifications
  - For each employee, name, signature and inclusive dates of employment
  - Errors and accidents and corrective action taken in response
  - Reports of unsatisfactory or mislabelled components or adverse reactions, including reports of investigation
  - All superseded SOPs and policies
  - Divided Responsibilities
- If two or more facilities are involved in collection and processing of a component, records must show the responsibilities of each.
- Each facility must provide a copy of any requested records to the final receiving facility except for those compromising donor confidentiality:
  - If two or more facilities participate in the collection, processing, or transplantation of the product, the records of each facility must show the extent of the responsibility
  - The collection facility must furnish to the facility of final disposition, a copy of all records relating to the collection and processing procedures performed in so far as they concern the safety, purity and potency of the product
- Maintenance records for equipment, including preventive maintenance
- Sterilisation of supplies and reagents
- Disposition of rejected supplies and reagents

iii. Quality Records to be maintained indefinitely:

- Calibration of Equipment
- Performance checks of equipment
- Periodic checks of sterile techniques
- Periodic tests of transport equipment
- Quality Control testing results, interpretation and corrective action for out of range values
- Results of external proficiency testing

5.2 **SAFETY AND ENIRONMENTAL REQUIREMENTS**

5.2.1 The facility must be operated in a manner to minimise risks to the health and safety of employees, patients, donors (patients with lines or the use of bed pans).

5.2.2 The facility must establish and maintain policies, processes and procedures designed to minimise risks to the health and safety of employees, donors, patients, volunteers and other persons affected within the work environment. Suitable facilities, environment and equipment must be available to maintain safe operations, National and local regulations apply.

5.2.3 Policies, processes and procedures must identify and address the hazards present in the facility, including biological, chemical and where applicable, radiation safety and appropriate intervention to mitigate exposure and must include a system for monitoring training and compliance.

5.2.4 Biohazardous materials must be handled and discarded in a manner that minimises the potential for human exposure to infectious agents.

5.2.5 Where liquid nitrogen is present, specific hazards must be addressed in the safety policies.

5.2.6 Facilities must be of adequate size and construction for the procurement, processing, preservation and storage of cells, tissues, and organ source material destined for use as or for processing into therapeutic products for in-vivo human use.

5.2.7 The facility must design, approve and implement an environmental control system that:

i. Optimises safety
ii. Ensures product integrity
iii. Minimises cross-contamination or accidental exposure to infectious disease agents

These conditions must be monitored

5.2.8 The degree of environmental monitoring must be appropriate to the cellular therapy product manipulation performed.

5.2.9 Access to facilities used for the procurement, processing, preservation and storage must be limited to authorised individuals.

5.3 **EQUIPMENT**

5.3.1 The facility must be furnished will all items of equipment for the provision of defined services.

5.3.2 The equipment must be capable of achieving the accuracy required.

5.3.3 The facility must establish and maintain policies, processes and procedures to control, maintain and monitor critical equipment.

5.3.4 The facility must establish a programme that regularly monitors and demonstrates proper calibration and function of equipment. The facility must have a documented and recorded system for preventive maintenance.

5.3.5 Manufacturer's instructions, operator's manuals or other documentation (were available) must be available.

5.3.6 Each item of equipment must be uniquely identified.

5.3.7 There must be a list of all critical equipment.

5.3.8 Equipment must be operated by authorised personnel.

5.3.9 The facility must define the process for the calibration of the equipment, including details of the equipment type, unique identification, location, frequency of checks, check method, acceptance criteria, limitations and the action to be taken when results are unsatisfactory.

5.3.10 Equipment must be safeguarded against adjustments that would invalidate the calibration settings.

5.3.11 The facility must define a process for when the equipment is found to be out of calibration or specification.

5.3.12 Calibrations must be performed using equipment and materials that have adequate accuracy and precision.

5.3.13 Calibration measurements must be traceable to the International System of Units (SI units) where possible.

5.3.14 When equipment is found to be defective, it must be taken out of use, clearly labelled and appropriately stored until it has been repaired and shown by calibration, verification or testing to meet specified acceptance criteria. The facility must examine the effect of the defect on previous examinations and institute corrective action.

5.3.15 The facility must take reasonable measures to decontaminate equipment prior to service, repair or decommissioning.

5.3.16 Equipment traceability: records must be maintained to permit the tracing of any given cellular therapy product to all equipment associated with the procurement, processing, storage and distribution of the cellular therapy product. Records must also be able to identify and recall any product associated with a specific piece of equipment.

5.3.17 Where computers or automation is in use, the facility must ensure:

i. The computer software, including that built into equipment, is documented and suitably validated as adequate for use in the facility
ii. Defined processes for system operation
iii. Procedures are established and implemented for the protection of the integrity of data at all times
iv. The computers and automated equipment are maintained to ensure proper functioning and provided with environmental and operating conditions necessary for maintaining the integrity of data

v. Computer programmes and routines are adequately protected to prevent access, alteration or destruction by unauthorised persons
vi. The facility must have alternative systems to ensure access to critical information and continuous operation of critical activities in the event that electronic data and computer assisted functions are not available

5.4 PROCESS CONTROL

5.4.1 The facility must ensure that activities that affect the quality of cellular therapy products and services are carried out under controlled conditions to prevent contamination of cellular therapy products, maintain the cellular therapy product's function and integrity and prevent the transmission of infectious diseases.

5.4.2 Controlled conditions must include:

i. The use of approved policies, process and procedures for all products and services
ii. Compliance with policies, process and procedures and all relevant standards
iii. Definition of criteria for acceptable results of in-process tests and final cellular therapy product characteristics
iv. Identification of the need for statistical techniques required for establishing, controlling and verifying process capability and product characteristics
v. Use and control of suitable equipment, materials and working environments
vi. Performance by qualified, trained and competent staff

5.4.3 The clinical outcome data and information on patient adverse events must be monitored and reviewed as part of an on-going quality management program. The sharing and review of these data must be defined in agreements.

5.4.4 **Change control:** the development of new or changed processes and procedures must be controlled. Quality requirements must be incorporated into the development of new or changed processes, products and services. Planning and implementation activities at a minimum must include the following:

i. Evaluation of accreditation, regulatory and legal requirements related to the new or changed process, product or service
ii. Review of current available knowledge
iii. Evaluation of risk
iv. Identification of affected internal and external parties and mechanisms to communicate relevant information
v. Identification of performance measures as applicable to the new or changed process, product or service
vi. Evaluation of resource requirements
vii. Evaluation of the impact of the new or changed process, product or service on other facility processes
viii. Evaluation of the need to create or revise documents for the new or changed process, product or service
ix. Review and approval of the output of process development and design activities
x. Evaluation of the extent and scope of process validation or re-validation depending on the level of risk and impact of the new or changed products or services

5.4.5 **Process validation:** prior to implementation, the new or changed process and procedure must be validated. The validation process must contain at least the following:

i. Identification of goals, expected outcomes and/or performance measures
ii. Criteria for review of outcomes
iii. Review of actual results
iv. Actions to be taken if goals are not met

5.4.6 **Process implementation:** the facility must plan and control the implementation of new or changed processes. Post implementation, evaluations of new or changed process and procedures must be performed.

5.4.7 **Change control:** the facility must identify the reasons for a change and obtain the appropriate approval before implementation. Any changes that may affect the safety,

purity, potency or efficacy of the cellular therapy product must be validated before the distribution and issue of products for administration.

5.4.8 **Quality control:** the facility must establish a program of quality control that is sufficiently comprehensive to ensure that materials, equipment and analytical procedures function as specified.

5.4.9 **Proficiency testing:** the facility must participate in a proficiency testing program for each analyte measured by the laboratory for determining the accuracy and reliability of results. Proficiency test outcomes must be reviewed and presented to staff. Investigation and corrective actions must be taken for any testing failures.

5.5 DONOR EVALUATION

5.5.1 Criteria for donor selection, evaluation and management by trained medical personnel must be in writing.

5.5.2 Donor evaluation procedures must be in place to protect the safety of the cellular product recipient.

5.5.3 In the instances of exceptions to the donor selection process arising, written approval of the medical director and recipient's practitioner must be obtained.

5.5.4 Collection of cellular therapy products from donors who do not meet criteria must be documented in the donor and recipient charts and used with the informed consent of the recipient.

5.5.5 The donor must be evaluated by the attending medical practitioner for potential risks during the collection procedure.

5.5.6 The risk of donation and informed consent must be documented.

5.5.7 Issues of donor health that pertain to the safety of the collection procedure must be communicated in writing to the Facility Staff.

5.5.8 Cellular therapy donors:

i. Donor eligibility

	Living Allogeneic Donor	**Autologous Donor**	**Mother of Cord Blood Donor**
Clinical Evaluation of Donor Suitability (protect safety of the donor)			
1. General health physical examination and health history	Yes	Yes	Yes
2. Haemoglobinopathy risk	Yes	Yes	NA
3. Anaesthesia risk for marrow donors	Yes	Yes	No
4. Peripheral venous access for apheresis donors	Yes	Yes	No
Pregnancy in female donors	Yes	Yes	No
Clinical Evaluation of Donor Eligibility (protect safety of the recipient)			
1. Physical evidence of risk for, or symptoms of, transmissible disease	Yes	No	Yes
2. Immunization/vaccination history	Yes	No	Yes
3. Travel history	Yes	No	Yes
4. Transfusion history	Yes	No	Yes
5. Body piercing	Yes	No	Yes
6. Haemoglobinopathy	Yes	Yes	Yes
History of behavioural risk for exposure to the following infectious agents or diseases			
1. HIV	Yes	No	Yes
2. HBV	Yes	No	Yes
3. HCB	Yes	No	Yes

4. HTLV (viable leucocyte-rick products only)	Yes	No	Yes
5. Treponema pallidum	Yes	No	Yes
6. Malaria (travel or resident in malaria-endemic areas)	Yes	No	Yes
7. CJD	Yes	No	No

Note**:** The donor must confirm that all the information provided is true to the best of his/her knowledge.

ii. Tests for transfusion transmissible infections:

Infectious agents or diseases	**Living Allogeneic Donor**	**Autologous Donor**	**Mother of Cord Blood Donor**
HIV 1 & 2	Yes	Yes	Yes
HBV	Yes	Yes	Yes
HCV	Yes	Yes	Yes
EBV	Yes	No	Yes
Treponema pallidum	Yes	Yes	Yes
NTLV 1 & 2 (viable, leukocyte-rich products only)	Yes	Yes	Yes
CMV (viable leukocyte-rich products only)	Yes	No	Yes
Malaria (travel or residence in malaria-endemic areas)	Yes	No	Yes
Toxoplasma	Yes	No	Yes
HLA Type	Yes	No	Yes
ABO/Rh	Yes	Yes	Yes
Complete blood count (for apheresis and marrow donors)	Yes	Yes	NA
Pregnancy test (female donors) immediately prior to G-CSF administration	Yes	Yes	NA

- Tests that must be performed: Hepatitis B Virus (HBsAG and anti-HBc), Hepatitis C virus (anti-HCV), HBV DNA HCV RNA, HIV 1 & 2 antibody, HIV-1 RNA, anti-HTLV 1 & 2 and serological test for syphilis.
- Any other tests that an independent medical practitioner may deem necessary after accessing the suitability of the donor to donate.
- Infectious disease testing must be performed in a manner that permits the timely determination of donor eligibility. For unrelated donors they must be performed within 30 days of donation and must be repeated on the day of donation

5.5.9 Donor records to be maintained indefinitely:

i. Autologous donors
- Identifying information
- Medical history, interview and physical examination
- Informed consent
- Interpretations of ABO group and Rh type and tests for infectious disease markers
- Adverse reactions and donor complaints

ii. Allogeneic or Syngeneic Marrow and Peripheral Blood Progenitor Cell Donors
- Donor identifying information
- Recipient identification sufficient to permit tracing of the component

- Records of medical history, interview and physical examination to be retained by transplant physician
- Informed consent to be retained by transplant physician
- Adverse reactions or donor complaints
- Interpretation of ABO group and Rh type, tests for disease markers, detection and identification of unexpected red cell antibodies and if performed, red cell compatibility testing with a sample from the intended recipient to be retained by transplant physician

5.6 CELLULAR THERAPY PRODUCT COLLECTION/PROCUREMENT

5.6.1 General

i. The collection team must be under the supervision of a licensed medical practitioner. Trained support personnel must be available at the facility where collection is performed.

ii. Before collection of is undertaken, a written instruction for the collection from the recipient's physician to the collecting service regarding scheduling and procedural details, including the end point of acceptable collection, must be provided.

iii. Before the collection of allogeneic cellular therapy product, the prospective donor's suitability must be documented by the transplant physician and should include HLA matching with the recipient (when applicable), infectious disease markers, ABO group and other test results.

iv. Methods of collection must employ aseptic techniques and must use procedures known to result in acceptable progenitor cell viability and recovery.

v. All reagents used for the collection procedure must be sterile. The cells collected must be packaged in a closed sterile container and labelled. Lot numbers and expiration dates of reagents and disposables must be recorded.

vi. Emergency medical care must be available to the donor.

5.6.2 Medical Management and Emergency Care of Donors

i. The availability of medical care must be based on the risks and clinical situation associated with each category of donation. Facilities procuring cells, tissues or organs from living donors must have provisions for emergency care and medical management of adverse events in those donors.

ii. Before procurement, the procuring facility must obtain final approval and documentation by the from the donor's medical practitioner that the donor is able to proceed with the donation.

iii. For any procurement procedure other than cord blood procurement, a designated individual at the procurement site must confirm that the donor's medical status permits procurement and document that the donor's health status is acceptable for donation.

iv. For mobilised donors (apheresis and marrow), a complete blood count, including platelet count must be obtained before mobilisation and within 24 hours before each procurement procedure. For non-mobilised donors and other donors who are haematologically stable, a complete blood count including platelet count must be obtained within 72 hours before the first procurement procedure and within 24 hours before each subsequent procedure during a continuous series of collections.

v. When a central venous access device is used for a procurement procedure, the following requirements must apply:
   - The device must be placed by a qualified person
   - Before procurement, the correct anatomic location of the access device must be confirmed by methods appropriate for the placement site.

vi. The administration of a pharmacologic or biologic agent(s) to the donor must be performed under the supervision of a licensed medical practitioner experienced in the use of said agent(s) and management of complications.

vii. Allogeneic and autologous donors must be evaluated for the risk of haemoglobinopathy before the administration of a mobilising agent.
viii. The administration of local anaesthesia to the donor must be performed under the supervision of a licensed medical practitioner. General anaesthesia must be administered under the supervision of a licensed anaesthesiologist.

5.6.3 Peripheral Blood

i. Haematopoietic growth factor administration must be under the supervision of the Transplant Physician.
ii. Central venous catheters must be placed under the direction of a licensed physician or surgeon qualified to perform the procedure.

5.7 HANDLING OF COLLECTED PRODUCT

5.7.1 As soon as possible after procurement, each organ, tissue component, or cellular therapy product must be packaged in an individually labelled container suitable for the specific product.

5.7.2 The facility must verify the accuracy of the procurement container labelling and donor identification in the proximity of the donor (in the case of cord blood procurement, the birth mother).

5.7.3 Procurement records must show:

i. Unique donor identification
ii. Date and time of procurement
iii. Name and address of procurement facility
iv. Pertinent details of procurement process
v. Identification of persons responsible for each step of the procurement
vi. Names, manufacturers, lot numbers and expiration dates of critical materials and reagents and quantities of reagents used in the procurement
vii. Identification of equipment used in the procurement.

5.7.4 The facility must establish and maintain policies, processes, and procedures that are intended to limit deterioration, prevent damage, ensure timely delivery and protect the quality of the materials and cellular therapy products during transport and shipping.

5.7.5 The facility must control packaging to the extent necessary to ensure conformance with specified requirements, local, national and/or international transport/shipping regulations apply.

5.7.6 Containers must be qualified at defined intervals to ensure that they maintain temperatures within acceptable range for the expected duration of transport or shipping.

5.7.7 When products are transported or shipped, the extent of temperature monitoring must be defined and must be appropriate to the duration of transport or shipping.

5.7.8 When cryopreserved products are shipped, the temperature of the shipping container must be monitored continuously.

5.7.9 The facility must label shipping containers and cellular therapy products in a manner designed to allow positive identification and to inform the carrier of the appropriate handling.

5.7.10 Product inserts and records must accompany products being shipped or transported between facilities. When the product is transported within a facility, product inserts and records must be readily available.

5.7.11 The receiving facility must have a designated area to receive the product.

5.7.12 At the time of receipt, incoming cells, tissues and organs must be inspected, sampled and/or tested, as appropriate, to determine their acceptability.

5.7.13 The receiving facility must maintain records of product acceptability. The following must be recorded:

i. Name of source material
ii. Name of supplier
iii. Unique product identifier, if required

iv. Date of receipt
v. Date of procurement, or manufacture
vi. Date of expiration, if required
vii. Results of inspection: product appearance, integrity of containers, temperature acceptability
viii. Identity of person receiving the product
ix. Indication of acceptance, quarantine or rejection

5.8 LABELS, LABELLING AND LABELLING CONTROLS

The facility must have policies, processes and procedures for labels and labelling of products and samples. As a minimum, the following shall be addressed:

- The acquisition and creation of cellular therapy product label templates.
- Verification that the label stock meets facility-defined specifications.
- The qualification, review and approval of labels before use.
- The controls in place to ensure proper cellular therapy product identification.
- The system for the discard of obsolete labels.

5.8.1 All containers of source material, in-process cellular therapy products and final products must be labelled appropriately.
i. Regulated investigation products must be labelled according to local and/or national regulations.
ii. Products approved or licensed by applicable local and/or national governments must be labelled according to the terms of licensure or approval.

5.8.2 Biohazard labels must be affixed to cellular therapy products that are positive for HBsAg and/or HIV.

5.8.3 Packaging and labelling – labelling information must be verified for accuracy and completeness at the following times, as a minimum:
i. Immediately after procurement
ii. Upon receipt at the facility involved in processing and storage
iii. At the facility-defined in-process steps, including transfer to a different storage location and removal/retrieval of attached segments and/or samples, if applicable.
iv. At the completion of processing and/or before storage
v. Before distribution or issue
vi. Before administration

THE REQUIREMENTS FOR THE LABELLING OF CELLULAR THERAPY PRODUCTS

ELEMENT	COMPLETION OF PROCUREMENT	IN-PROCESS LABEL	COMPLETION OF PROCESSING	DISTRIBUTION AND ISSUE
Unique alpha and/or numeric identifier of the product	P	P	P	P
Name of the product and modifiers	P	P	P	P
Donor identification of name	A	NA	A	A
Date of procurement	R	NA	R	R
Time of completion of procurement	R	NA	R	R
Name of procurement facility/donor registry	R	NA	R	R
Approximate product volume or weight (if applicable)	R	NA	R	R
Names/volumes of anticoagulants and other	R	NA	R	R

additives (if applicable)				
For patient-specific products, recipient name and/or identifier	R	R	R	R
Expiration date and time	NA	NA	A	A
ABO and Rh of the donor (if applicable)	NA	NA	R	R
Red cell compatibility (if applicable)	NA	NA	NA	R
Recommended storage temperature	R	NA	A	A
Name and address of the facility making the product available for distribution	NA	NA	R	R
Biohazard Label	A	A	A	A
Phrase: Do not Irradiate (if applicable)	NA	R	R	A
Phrase: Not evaluated for infectious substances and Warning: Advise patient of communicable disease risks (if applicable)	A	A	A	A
Phrases: Warning: Reactive test results for (name of disease agent or disease) and Warning: Advise patient of communicable disease risk (if applicable)	A	A	A	A
Phrase: Do not use Leukoreduction Filters (if applicable)	NA	NA	A	A
Phrase: For Autologous use only (if applicable)	A	A	A	A
Phrase: For use by intended recipient and product	NA	A	A	A
Phrase: Properly identify intended recipient and product	NA	A	A	A
Phrase: For clinical use only (if applicable)	NA	A	A	A

KEY: P – Permanently affixed
A – Attached (may be permanently affixed)
R – Accompanying records
NA – Not applicable

NOTE:

- The in process label may be used during process and prior to distribution and issue.
- The final labelling information for distribution must be on or included with the container before the product is issued or transported.
- In cases where donor anonymity must be preserved, this information is not required.
- If affixing or attaching the applicable warnings and statements to the container is physically impossible, the labelling must accompany the human cells, tissues and cellular therapy products.

THE REQUIREMENTS FOR LABELLING SHIPPING CONTAINERS

ELEMENT	SHIPPING DOCUMENT	OUTER SHIPPING CONTAINER
Biohazard Label (if applicable	R	NA
Phrase: Do not irradiate (if applicable)	R	A
Phrase: Do not x-ray (if applicable)	R	A
Phrases: Medical specimen or Human cells for transplantation or equivalent.	NA	A
Date of distribution	R	A
Name and street address of receiving facility	R	A
Name and phone number of contact person at receiving facility	R	A
Name, street address and phone number of the shipping facility	R	A

KEY: R – Accompany records
NA – Not applicable
A – Affixed or attached

NOTE:

- Shipping documents must be placed within the shipping container

5.9 CELL PROCESSING

5.9.1 General policies

i. A written request specifying the product type, recipient and donor identifier, the type of processing that is to be performed and the anticipated date of processing from the patient's attending physician for specific processing of PBSC's before such processing is initiated, must be documented.

ii. The medical director or designee must review the processing record for each component in a timely manner.

iii. The medical director or designee must notify the patient's physician if defined endpoints of the processing procedure are not met and if clinically significant procedural variances occur, including the corrective action taken. Notification must be documented.

iv. Processing methods must employ aseptic techniques and must be those that have been demonstrated to result in acceptable progenitor cell viability and recovery. Whenever possible, preference must be given to the use of reagents and supplies approved for human use. A system must be in place to document the person responsible for each step of the processing methods.

v. Policies, processes and procedures used during the cellular therapy manipulation must address the following:

- Staff attire, gowning and use of personal protective equipment
- The use of biologic safety cabinets or other environmentally controlled spaces (if applicable)
- Materials and equipment for each specific process
- Manipulation of materials
- Critical calculations
- Transfer of source material, cellular therapy products, media or reagents between containers
- Sampling of source material, cellular therapy products, media, reagents or other materials used in product manipulation
- Acceptable control limits for temperature and humidity
- Disposition of cellular therapy by-products and waste

vi. The procurement and processing facilities must establish and maintain policies, processes and procedures designed to minimise contamination of the product. The following must be addressed:
- Environmental controls and monitoring commensurate with the risk of product contamination
- Process controls
- Staff training in aseptic technique
- Laboratory attire
- The effectiveness of such measures must be monitored and reviewed on a regular basis

vii. Operational controls must prevent mix-ups and cross-contamination. The following must be defined:
- Movement and storage of materials (including waste) and equipment and workflow within workspaces
- Physical and/or temporal segregation of equipment or materials
- Physical and or temporal segregation for processing different cellular therapy products or cellular therapy product lots
- Use and storage of materials that may adversely affect the quality of the cellular therapy product
- Cleaning and setup of spaces or equipment between production runs
- Labelling processes
- Clerical identification checks at critical steps

viii. Policies, processes and procedures must be in place to prevent the unintentional irradiation or unintentional leukocyte reduction filtration of cellular therapy products.

5.9.2 Processing records to be maintained:

i. Physician authorisation for collection and processing.
ii. Unique donor identification
iii. Component name, unique alphanumeric identification, preparation volume and additives, date of collection and date of processing.
iv. Names of persons responsible for each step
v. Details of component processing including results.
vi. Measurements of established collection and processing parameters.
vii. Documentation of manipulations other than minimal.
viii. Name, lot number and expiration date of all reagents and supplies used during processing.
ix. Documentation of labelling, including initials of personnel performing any container transfer.
x. Two independent verifications of the accuracy of the final container label prior to issue.
xi. Documentation of product distribution or final disposition

5.10 DETERMINATION OF ACCEPTABLE VALUES OR RANGES

The facility must define test methods and acceptable values or ranges for defined critical characteristics for each product.

5.10.1 Laboratory testing

i. Component testing
- Microbial contamination of cellular therapy products must be monitored and documented. Positive results must be investigated. The medical director or designee is responsible for reviewing of the results.
- Regarding the management of cellular therapy products with positive microbial culture results, the facility of final distribution must have policies and procedures to ensure:

- Product labelling
- Investigation of cause
- Notification of recipient medical practitioner
- Notification of donor's medical practitioner
- Recipient follow up and outcome analysis
- Reporting to regulatory agencies, if appropriate.

5.11 **STORAGE**

5.11.1 Storage

i. **Liquid state storage:** cellular therapy products stored in the liquid state must be maintained within a validated temperature range that will ensure the viability of the cells.

ii. **Frozen state storage:** The acceptable storage temperature range must be determined to be appropriate for the cryopreservation agent being used for cell freezing. The temperature range for each agent used must be defined.

iii. For components immersed in liquid nitrogen, procedures must be in place to minimise the risk of microbial cross-contamination of individual components.

5.11.2 **Storage Devices and Inventory Control**

i. Storage device compartments in which cellular therapy products are stored must be of a capacity and design to ensure that the proper temperature is maintained.

ii. The storage device must have a specified inventory system to ensure cellular therapy product placement within the storage device.

iii. The inventory control system must be able to locate any component or quality control vials from that component. It must include the donor name, identification number, recipient name, date of collection, storage device, location of component or vials within the storage device, number of containers for the component, number of containers or vials dispersed, dates of issue and number of containers or vials remaining.

iv. Periodic review of the inventory system must be performed and documented.

v. Documented procedures must define alternative methods of storage, or precautions to be used for storage of disease marker positive components and untested components, in order to minimise the likelihood of cross-contamination.

vi. Materials known to adversely affect cellular therapy product may not be stored in the same storage devices with cellular therapy product.

5.11.3 **Storage monitoring**

i. Refrigerators, mechanical or electrical freezers and storage devices using the vapour phase of liquid nitrogen for cellular therapy product, must have a system to monitor the temperature continuously and to record the temperature at least every 4 hours.

ii. **Storage in liquid nitrogen:** freezers must have a mechanism to ensure that levels of nitrogen are maintained and documented on a defined periodic schedule. For storage in the liquid phase, the level in the storage device must be maintained at a height to ensure continuous immersion of cellular therapy products during storage.

iii. The storage device must be located in a secure area and should be locked when the area is not staffed.

iv. Storage devices must have continuously active alarm systems.

v. If laboratory staff are not always present in the immediate area of the storage device, a remote alarm device must signal in an area that has adequate staff to ensure that immediate action is taken.

vi. The emergency alarm must be set to activate a temperature or unsafe level of liquid nitrogen that will allow proper action to be taken before the PBSC's reach undesirable temperatures and to all time to salvage components.

vii. Records to be maintained indefinitely:

- Release from Quarantine Records

- Documentation of quality assurance and technical review of the donor chart
- Documentation of medical director's review and approval
- Documentation of authorisation to release any component with a positive Infectious disease marker tests
- Documentation of inspection of the container at the time of issue
- Storage Records and Distribution Records
- Records of reissue, including temperature records
- Final disposition of each component
- Record of total inventory of stored components at any given time

- Records to be maintained for a minimum of 10 years:
  - Storage temperature charts and records, including temporary transport storage

5.12 **CRYOPRESERVATION**

5.12.1 Cryopreservation procedures

i. Cryopreservation procedures must be validated.

ii. The documented procedures must specify the starting cell component, the cryoprotectant solution, the range of cell concentrations, the cooling rate, the endpoint temperature of cooling and the storage temperature. If a rate-controlling device is used for cryopreservation, the cooling rate must be monitored and a copy of the cooling graph must be maintained for each procedure. If a rate-controlling device is not used, the method must be validated and the validation records maintained. Recovery and cell viability have to be validated beforehand and the consistency or reproducibility must be validated.

5.12.2 Cryopreserved sample aliquots

i. Sample aliquots of components, cryopreserved and stored under the same conditions as the Cellular Therapy Products, should be retained for possible future testing.

5.12.3 Special requirements for cord blood: cord blood products must have at least two integrally attached segments cryopreserved with the product. The identity of the product and segment must be confirmed by two individuals when integrally attached segments are removed.

5.13 **ISSUE**

5.13.1 A medical order must be received by the facility for the issuing of the product.

5.13.2 The release from storage must be documented by numeric or alphanumeric identification for each collection, date and time, recipient name and identification number, the facility and person to whom the cells were dispensed and the integrity of the container and label.

5.13.3 Each container must be inspected to ensure that the container is intact and the label is complete, securely affixed and legible. Identification must be verified by two individuals or one individual and an electronic device that has been validated to fulfil the labelling identification function(s). The inspection must be documented.

5.13.4 A mechanism must be in place to document the identification of the person/s removing the cellular therapy product from storage, delivering of cellular therapy product to the site of infusion and the administering of the infusion.

5.13.5 With regards to PBSC and cord blood, documented procedures must be in place to prevent the inadvertent irradiation of the cellular therapy product.

5.13.6 Before release to the treating physician, the following test results must be made available:

i. ABO and other blood group and type antigen compatibility, if applicable.

ii. HLA compatibility, if applicable

iii. A list and interpretation of results of all microbial testing done on the cellular therapy product.
iv. A listing and interpretation of results of all microbial testing done on the cellular therapy product
v. For allogeneic products: a statement that the donor has been determined to be eligible or ineligible, noting the name and address of the facility that made the donor eligibility determination. For product form an ineligible donor, a statement noting the reasons for the determination of ineligibility.

5.14 TRANSPORTATION

5.14.1 Transportation between facilities; if a cellular therapy unit is intended to be transferred to another facility, mutual agreement regarding temperature and duration of storage must be reached and documented prior to the cellular therapy product being transferred.

5.14.2 Documented procedures must define the transportation that is consistent with the irreplaceable nature of the components, limit deterioration and protect the quality of the product, prevent damage and ensure timely delivery. The mode of transportation selected must be determined by special shipping and handling requirements of the components and/or shipping refrigerants, shipping restrictions of commercial carriers and the urgency of the request.

5.14.3 The facility must control the packaging to ensure conformance with specific national and international requirements.

5.14.4 Transport containers must be qualified at defined intervals to ensure that they maintain temperatures within the acceptable range for the expected duration of the transport.

5.14.5 The extent of temperature monitoring must be defined and must be appropriate for the duration of the transportation or shipping. When cryopreserved products are transported, the transport container must be continuously temperature monitored.

5.14.6 The facility must label transport containers and cellular therapy products in a manner designed to allow positive identification and to inform the carrier of the appropriate handling.

5.14.7 All product inserts and records must accompany the product during transportation.

5.14.8 The receiving facility must maintained records of product acceptability.

5.15 ADMINISTRATION

5.15.1 The administration of cellular therapy product must occur under direct or indirect supervision of the transplant physician and, if under the indirect supervision of the transplant physician, under the direct supervision of a registered professional nurse.

i. Positive identification of the recipient and the cellular therapy product container by two individuals must be documented. Immediately before administration, the infusionist must verify and document that all information identifying the container with the intended recipient has been matched in the presence of the recipient, item by item.

5.15.2 The recipient must be observed during the administration and for an appropriate time thereafter.

5.15.3 Vital signs must be recorded at least immediately before and after administration.

5.15.4 All identification attached to the container must remain attached at least until the administration has been terminated.

5.15.5 With regards to PBSC's and cord blood, they must be administrated through sterile, pyrogen-free tubing using an administration set without a filter. E.g. Leukocyte-reduction filters or micro aggregate filters must not be used.

5.15.6 There must be documented procedures for the return to inventory of cellular therapy products issued for infusion, but not infused.

5.15.7 An infusion record must be completed for each component infused, indicating the recipient's name, identification number, ABO group and Rh type (in the case of

allogeneic transplants), the unique donor identifier, the donor's ABO group and the Rh type and the date and time of infusion.

5.16 **ADVERSE REACTIONS**

5.16.1 The facility where the administration of the cellular therapy product takes place must have documented procedures for the management of potential adverse reactions during or following the administration, including a list of emergency medications and supplies that must be available immediately.

5.16.2 Records of any reports of adverse reactions must be maintained

5.16.3 The medical director is responsible for ensuring that an investigation of each reported adverse reaction is made.

5.16.4 A written report of the investigation of adverse reactions, including conclusions and outcome analysis, must be prepared and maintained as part of the record for that component. Copies of this report must be forwarded to and maintained by each facility involved in the preparation of the cellular therapy product.

5.17 **RETURN OF CELLULAR THERAPY PRODUCTS**

5.17.1 Cellular therapy products accepted for return must meet the following criteria:

i. The integrity of the primary container may not have been compromised.

ii. The cellular therapy product must have been maintained, subsequent to issue at the specified temperature range during storage and transportation.

iii. If the above criteria have not been met, the processing facility may not accept the product unless the processing facility director or designee gives specific authorisation to accept the product for return to inventory after determining the product acceptability.

iv. The processing facility director or designee must consult with the recipient's medical practitioner regarding reissue or disposal of the returned product.

v. Records of the events requiring return, the results of inspection upon return and subsequent action taken to ensure product safety and viability must be maintained.

5.18 **DISPOSAL**

5.18.1 The disposal of cellular therapy products must comply with written policies.

5.18.2 Patient death must be documented, including any directive regarding further need for the product before any product is discarded.

5.18.3 Prior to collection, a written agreement between the storage facility and the donor or donor's legal representative, or the patient or the designated recipient, as appropriate, defining the length of storage and the circumstances for disposal or transfer of cellular therapy products, must be concluded.

5.18.4 If the patient or designated recipient is still alive at the time of disposal specified by the written agreement, the patient must be offered the opportunity to transfer the product to another facility.

5.18.5 If there is no pre-existing agreement describing conditions for product storage and/or discard, the storage facility must:

i. Communicate with the designated recipient's medical practitioner regarding the continuing need for the storage of the product.

ii. Make a documented effort to notify the patient or designated recipient about product disposition or disposal.

iii. Dispose of cellular therapy products obtained through donor registries in accordance conditions mutually agreed upon by the storing facility and the donor registry.

iv. Approve, through the Processing Facility Medical Director, in consultation with the recipient's medical practitioner, the product discard, disposition, or method of disposal.

v. Ensure that the method of disposal and decontamination meet governmental regulations for disposal of biohazardous materials and/or medical waste; and that
vi. Indicate on the records for discarded products whether the product was discarded, date of discard and disposition of product or method of disposal.

5.19 **DISCARD OF CELLULAR THERAPY PRODUCTS AND RELEASE FOR RESEARCH PURPOSES**

5.19.1 Prior to the collection, processing and/or storage of cellular therapy products, an agreement between the donor, the intended recipient,(with the exception of altruistic cord blood donation), the transplant physician and the cellular therapy collection/processing facility as to the specifics of the duration and conditions of storage and the indications for discard of the cellular therapy product, must be included.

5.19.2 A written policy for the discard of cellular therapy product or release for research purposes must exist.

5.19.3 The medical director in consultation with the transplant physician must approve in writing of the discard of cellular therapy product or release for research purposes and is responsible for documentation of the method and date of discard or date and disposition if released for research purposes.

5.19.4 The method of disposal and decontamination must meet all applicable laws and regulations for the disposal of human tissue.