International Standards for Therapeutic Apheresis Units (TAU)

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Table Of Contents

INTRODUCTION

Apheresis Medicine (AM) is that discipline of the medical arts and sciences concerned with the care and management of patients and donors involved in extracorporeal blood separation interventions used in the treatment of disease or in the collection of various blood constituents. It can arbitrarily be subdivided into three major care areas based on the status of the individual receiving the apheresis intervention: therapeutic apheresis (TA) where the individual is a patient being treated for a disease; donor/preparative apheresis where the individual is serving as a source of various blood products/derivatives for use in others; and donor/patient apheresis where the individual serves as the source of various blood-derived products for either allogeneic or autologous therapeutic use. Apheresis procedures associated with the latter two care foci are extensively regulated with facilities and organizations performing them typically being periodically assessed and certified by knowledgeable professionals. In contrast the area of TA has much more limited regulatory scrutiny typically performed in a limited manner by various clinically focused professional organizations where the major emphasis is on non-apheresis clinical care operations.

TA includes a wide range of therapeutic procedures that are based on the separation of blood components with subsequent removal of unwanted plasma or cellular components involved in the etiology of various hematologic, renal, neurological, and medical diseases in patients in whom other therapeutic approaches are totally or partially ineffective, sometimes not tolerated.

In Italy on an annual basis about 14,000 plasma-exchange treatments are performed per year using therapeutic apheresis procedures with approximately 7,000-8,000 photopheresis/extracorporeal photochemotherapy procedures also performed in patients with such conditions as graft versus host disease, or for the prevention or treatment of solid organ rejection, or in individuals with rapidly evolving auto-aggressive diseases and/or those refractory to established immunosuppressant regiments, or in patients with cutaneous T-cell lymphomas. Such a high rate of application of these forms of treatment translates to a procedural frequency that, when compared to the general Italian population, approximates to about 1 therapeutic apheresis procedure per year per every 2,900 residents. A frequency of this magnitude, if extrapolated on a European scale, would suggest that the number of TA procedures per year would equal approximately 170,000 TA treatments in all European countries combined. Even if reassessed by taking into account the different levels of technological availability in the various countries, the total aggregate number of TA interventions could still approach approximately 100,000 procedures per year.

As previously alluded to these therapeutic procedures can be characterized as a series of treatment sessions of high complexity that require the participation of staff with appropriate technical and nursing skills and medical expertise, the need for appropriate and pertinent documentation regarding the interventions, as well as dedicated facilities with organizational structures able to ensure operational efficacy, efficiency and patient safety. Specific skillsets and training requirements regarding the various practitioners in this field

exist and in conjunction with advances in medical knowledge related to apheresis medicine help ensure continual enhancements in patient safety for those needing this therapy.

One source for continued knowledge advancement regarding the clinical indications for the use of therapeutic hemapheresis is the periodically updated Special Issue on the Clinical Applications of Therapeutic Apheresis: An Evidence Based Approach produced by American Society for Apheresis (ASFA) and published in its official organ, the Journal of Clinical Apheresis.

With the goal of establishing an organizational model that allows for the best application of existing knowledge and technology and to ensure safety, effectiveness, and efficiency for any and all pertinent therapeutic procedures, in a manner of continuous quality improvement, the construction of a document to help guide discussions regarding the formulation of standards is beneficial. Such models have been achieved by others with much success including the development of international standards regarding cellular therapies promulgated by the JACIE-FACT (Joint Accreditation Committee ISCT-EBMT) – Foundation for the Accreditation of Cellular Therapy) collaborative which have been created and applied for standardization in the collection and clinical use of hematopoietic stem cells for transplantation. Such an approach in the construct of an organizational model pertinent to TA activities seems reasonable and desirable.

It is in this context that the Società Italiana di Emaferesi e Manipolazione Cellulare (SIdEM), in collaboration with the sector company Exem Consulting, has created a document regarding standardizations pertinent to TA: The International Standards for Therapeutic Apheresis Units (Standards TAU, Therapeutic Apheresis Units). It is hoped that such a document will facilitate discussions and actions in the international community leading to the construction of national organizational and quality models for facilities involved with TA activities and that in the near future, such a model based on these Standards could serve as a European operational frame of reference supporting a culture of and for patient safety and the continuous quality improvement in this therapeutic area. These International Standards have been created by a team of professionals and experts with the sole aim of identifying all the required information to ensure that facilities involved in TA may follow uniform and traceable operational guidelines engendering a continuous commitment to enhancing patient safety in TA.

It is envisioned the this document will serve as an operational tool that allows, in all centers of therapeutic apheresis, the introduction of a full-quality organizing model which may also, if appropriate, be integrated into any complete or partial organizational models already adopted and in use in those facilities. As such the Standards for TAU have been designed to define organizational structure requirements, procedures, and general management strategies that all therapeutic apheresis centers should follow to aid in the construction of an appropriate system of quality assurance, consistent monitoring, observation and the establishment and nurturing of a quality culture related to TA.

We believe that the implementation of these Standards will help ensure consistency in the management of patients, in the set up and performance of TA procedures, and guidelines for the proper recording and documentation of performed activities, based on functional and quality requirements developed and shared by AM professionals at national and international levels and in various educational forums.

The International Standards for TAU was designed to identify and define the minimum necessary organizing guidelines for centers performing therapeutic apheresis and are not intended to replace any regulations, laws, and national and international regulations currently in force in countries in which it may be applied. It is hoped that each TAU center which implements these standards will find them useful in the construction of a high quality TA management system that engenders a culture of continuous quality improvement with a focus on ever enhancing patient safety in the area of AM.

A. PART A: TERMINOLOGY AND ABBREVIATIONS, DEFINITIONS

A.1 TERMINOLOGY AND ABBREVIATIONS

AM: Apheresis Medicine

TAU: Therapeutic Apheresis Unit

RAQ: Quality Manager

QMS: Quality Manager Supervisor

TA: Therapeutic Apheresis

ITU: Immunotrasfusional Unit

SOPs: Standard Operating Procedures

BMT: Bone Marrow / Hematopoietic Precursors Transplantation

TTP: Thrombotic Thrombocytopenia Purpura

PPE: Personal Protective Equipment

AREA: A physical space not bounded which is part of a room.

ROOM: An enclosed area with limited/controlled access.

EQUIPMENT: All technological devices used in the TAU, whose operational failure may have a critical impact on patient safety.

MATERIALS: All products, reagents, drugs, plasticware kits, and liquids used in the TAU in the management of patients receiving an apheresis intervention.

CVC: Central Venous Catheter

A.2 DEFINITIONS

Biological products: Products obtained by a process of therapeutic apheresis and subsequently processed, manipulated, and/or treated before being assigned for direct reinfusion to the patient.
Online product: Product obtained by apheresis using a “closed system” process (i.e., without detachment from or interruption of the collection circuit and used in subsequent treatment, e.g.: Photopheresis).

Offline product: Product obtained by apheresis using an “open system” process (i.e., with detachment from or interruption of the collection circuit and used in subsequent treatment, e.g.: Extracorporeal photochemotherapy).

Critical Performance Measure (CPM): Any deviation involving processes, procedures, products, reagents, and kits potentially causing a danger to patients or personnel performing the apheresis. Periodic auditing and validation of such parameters with pertinent documentation is mandated.

B. Part B: TAU GENERAL REQUIREMENTS

B.1 TAU ORGANIZATION

B.1.1 TAU personnel consist of a team of medical, nursing, and where applicable, technical staff. Clinical leadership of the team is provided and coordinated by a medical director who is a physician knowledgeable in all pertinent facets of AM.

B.1.1.1 An organizational diagram depicting all involved staff and reporting relationships in the context of the larger facility/hospital structure shall be constructed.

B.1.1.2 A TAU shall offer/perform any or all of the following procedures:

B.1.1.2.1 Therapeutic Cytapheresis;

B.1.1.2.2 Plasma/Red Cell Exchange;

B.1.1.2.3 Hemo/Plasma Treatment;

B.1.1.2.4 Photopheresis/Extracorporal Photochemotherapy.

B.1.2 The TAU shall adhere to all applicable laws and regulations and institutional guidelines of the facility in which it is located.

B.1.3 TAU involved in any cellular therapy interventions shall abide by the current FACT-JACIE International Standards pertinent to the performance of all apheretic procedures for BMT.

B.1.4 For accreditation purposes, according to these Standards, each TAU shall perform, at least, 100 TA procedures; or at least 100 apheresis procedures with no less than 50 TAs if productive apheresis procedures on patients (i.e., hemopoietic progenitor collections, HPC, collections) are also performed per calendar year.

B.1.5 For accreditation purposes, according to these Standards, TA performance may be provided during routine business hours but for pathologies in which AT is a mandatory and/or an emerging treatment (i.e., TTP, acute chest syndrome in drepanocytosis, leukemic hyperleukocytosis with leukostasis, and hyperviscosity syndrome clinically expressed) each TAU shall offer 24-hours /7 days/week/ 365 days/year service for emergent/urgent TA interventions.

B.2 FACILITY REQUIREMENTS

B.2.1 The TAU shall have the appropriate space and areas to be able to adequately and safely perform all therapeutic activities related to:

B.2.1.1 Compliance with safety requirements for patients and personnel;

B.2.1.2 Protection of patient privacy;

B.2.1.3 Minimisation of risk of errors or cross contamination;

B.2.1.4 Allowance for easy cleaning, sanitization and ordinary or extraordinary maintenance of rooms, devices and instruments used in the TA intervention.

B.2.2 The following shall be ensured:

B.2.2.1 Room suitability before use, after periodical maintenance control or after introducing relevant changes.

B.2.2.2 Maintenance of appropriate ambient environmental humidity and temperature conditions.

B.2.2.2.1 Appropriate heating/air conditioning/ventilation systems/conditions/features must be provided and described in a pertinent SOP.

B.2.3 The TAU shall have adequate space and physical locations pertinent to the number and type of procedures offered and for the safe and efficient performance of these activities.

B.2.4 Access to TAU areas and rooms shall be restricted only to authorized personnel.

B.2.5 The TAU shall have, at minimum, the following clearly distinguished areas and locations:

B.2.5.1 Patient reception and registration areas;

B.2.5.2 A designated area for the provision of patient care in compliance with privacy requirements for confidential medical evaluations, clinical care, and medication administration;

B.2.5.3 Rooms or areas adequate to administer therapeutic treatment with, at least, two beds/chairs and a pediatric area, where appropriate;

B.2.5.4 Separated personal cleaning care facilities for patients and TAU staff;

B.2.5.5 A storage area for materials and primary used drugs;

B.2.5.6 An appropriate area for preparation of replacement solutions and for the manipulation of apheretic products for rapid reinfusion in compliance with requirements of sterility and cleanliness;

B.2.5.7 A storage area for rapid access to frequently/recently used documents and records; and

B.2.5.8 An appropriate area for the discarding of used apheretic products/materials and patient derived biological waste materials.

B.2.6 The TAU shall have written procedures for the cleaning, sanitization and maintenance management of rooms used in patient care activities.

B.2.7 The TAU shall define an emergency action plan to be implemented in cases of chemical, physical, biological, or nuclear environmental contamination.

B.3 SUPPORT SERVICES

B.3.1 The TAU shall be included in a Hospital with the following facilities:

B.3.1.1 An Immunohematology Laboratory and/or Transfusion Service;

B.3.1.2 A Diagnostic Laboratory offering clinical chemistry and microbiology testing;

B.3.1.3 Intensive care areas and recovery rooms.

B.3.2 The TAU shall define the scope of its services offered including types of procedures and the routine and emergency business hours when services are offered. Expectations regarding the involvement of other facility support services (e.g., CVC placement teams) during the evaluation for and performance of therapeutic procedures shall be identified and coordinated.

B.3.3 The TAU shall define the procedure for rapid access admissions to intensive care areas in cases of emergency.

B.3.4 If the TAU does not have an internal Immunotransfusion service and/or a diagnostic laboratory, it shall have a written agreement with an external facility defining the provision of these services.

B.3.4.1 Initial validation and on-going monitoring of service providers shall be documented and periodically reviewed for problems and remedies of any deficiencies if found.

B.4 TAU EQUIPMENT

B.4.1 TAU equipment shall be adequate with regard to the type and number of services provided.

B.4.2 A separate apheresis machine shall be reserved as a backup device for use in situations of primary equipment failures or to meet excess service demands during high patient census times

B.4.3 A supplemental oxygen device shall be available at each bed/chair position in the TAU.

B.4.4 The TAU shall have standard emergency equipment available (i.e., Code Crash Cart) providing pertinent drugs and devices along with a dedicated cardiac defibrillator. As an alternative to requiring the presence of cardiac defibrillator device, immediate telephonic access to the emergency team and their equipment is allowed.

B.4.5 The TAU shall have a SOP for the management of all pertinent equipment describing their control, availability, expiration dates, ordering/supply and maintenance responsibility of emergency equipment drugs and devices.

B.4.6 Documentation of conformity of emergency equipment shall be certified per individual institutional guidelines at least annually.

B.4.7 All TAU equipment shall be validated for their intended use

B.4.7.1 In case of malfunction or extraordinary maintenance requirements equipment shall be re-validated before reintroduction into the active service use.

B.4.7.2 Documentation of these activities shall be available for review/action as needed.

B.4.8 Electrical equipment shall have a back-up power supply system that ensures the maintenance of activity even in the absence of routine electricity supply in the overall network.

B.4.9 The TAU shall list and maintain records of all critical equipment, in particular:

B.4.9.1 Instrument location;

B.4.9.2 Handbook location;

B.4.9.3 Instrument access documentation;

B.4.9.4 Review of previous and latest instrument maintenance records; and

B.4.9.5 Entire documentation of instruments activity.

B.4.10 Each apheresis device should be given a unique device identifier.

B.4.10.1 An equipment register shall be maintained and periodically reviewed to ensure functionality of all devices and equipment.

B.4.11 The TAU shall define a procedure for monitoring instrument/device workload.

B.4.11.1 Crosschecks of the records of the instrument/device with the procedures performed with them should be documented,

B.5 TAU SAFETY

B.5.1 The TAU shall operate in a manner designed to minimize risk to the health and safety of patients, personnel, visitors and volunteers.

B.5.2 The TAU shall have a written safety manual that includes instructions for action in cases of exposure to communicable diseases or to chemical, biological or radiological hazards.

B.5.3 The TAU shall have a written procedure, that adheres to national laws and requirements, for biohazard waste disposal and protection of personnel from contamination.

B.5.4 All Personnel shall wear all pertinent PPE while performing procedures in the TAU.

B.6 EXTERNAL AGREEMENTS

B.6.1 The TAU shall develop contract agreements/arrangements with individuals/external facilities that have a relevant involvement in TAU activities e.g., on-call coverage by non-TAU physician and nursing staff.

B.6.2 Agreements shall include descriptions of the roles and responsibilities of each party.

B.6.2.1 Appropriate certification regarding the training, clinical experience, and competencies of the contracted staff shall be documented and reviewed at least annually.

B.6.2.2 Any pertinent institutional specific requirements regarding such staff shall be identified and documented before such individuals undertake clinical care responsibilities.

B.6.3 Agreements shall be dated and signed by the responsible person(s) (e.g., Medical Director, Departmental Chief etc.) and revised at least once every two years.

B.6.4 Facility supplier relationships (e.g., general supplies), which are managed by Hospital Administration, are not subject to these requirements.

B.6.5 The TAU shall have a SOP that describes policies and procedures for patient admission and management that shall be shared with pertinent department/ward entities. A reference physician shall be identified to interact with the TAU staff in cases of urgent and routine communications.

B.6.6 If an Immunotrasfusional Unit (ITU) is not included in the facility in which the TAU is located, there shall be an agreement describing arrangements with an external ITU (organizational, management of blood products etc.) for the provision of all pertinent blood products and derivatives.

B.7 TAU PERSONNEL ORGANIZATION

B.7.1 General

B.7.1.1 The TAU team shall include at a minimum the following professionals:

B.7.1.1.1 TAU Medical Director;

B.7.1.1.2 Medical Staff;

B.7.1.1.3 Nursing Staff ;

B.7.1.1.4 Technical Staff;

B.7.1.1.5 Quality Manager.

B.7.1.2 The TAU shall have a SOP describing an organizational chart defining roles and responsibilities of its various personnel. Relationships with other clinical services (e.g. Surgery, Nephrology, Interventional Radiology, etc. for intravenous access device placement) and contracted service vendors shall be documented.

B.7.1.3 For services/activities unavailable in the TAU, the TAU shall develop arrangements and contract agreements with external facilities/entities to obtain such services/activities as required for the performance of its operations.

B.7.1.4 Agreements can be contracted with individuals/entities provided there are no conflicts of interest involving the pertinent parties.

B.7.2 TAU MEDICAL DIRECTOR

B.7.2.1 The TAU Medical Director shall meet the following minimum requirements:

B.7.2.1.1 Medical License to practice.

B.7.2.1.2 Certification of higher specialist training in Hematology/Transfusion Medicine/Nephrology or other medical specialties and two years of documented experience in TA.

B.7.2.2 The TAU Medical Director shall have the following training/experience:

B.7.2.2.1 During the 12 months prior to the accreditation period he/she must have supervised at least 100 apheresis procedures. If productive apheresis procedures are to be included (i.e., HPC collections) then of the total 100 TA procedures, at least 50 TA procedures must be have been performed with the remainder being able to be achieved by any combination of productive apheresis procedures and TA procedures on patients being performed during the 12 months prior to the accreditation period.

B.7.2.3 The TAU Medical Director shall be responsible for:

B.7.2.3.1 Oversight of all clinical activities, quality management/improvement activities, and operational administration of clinical services supplied by the TAU for patients during the peri-apheresis care period (including initial evaluation; treatment sessions, post-therapy follow-up and monitoring for adverse complications) ;

B.7.2.3.2 Oversight of all TAU personnel training and evaluations;

B.7.2.3.3 Oversight of the management of all TAU procedures;

B.7.2.3.4 Oversight of the TAU Quality Management System especially as it pertains to national and international laws and requirements.

B.7.2.3.5 Oversight of the management of the relationship between the TAU and its facility administration.

B.7.2.4 The TAU Medical Director shall participate regularly in scholarly educational activities related to the field of TA (courses, congresses, scientific publications/ research paper, etc.) to give evidence of continuous self-directed education in the discipline of Apheresis Medicine.

B.7.2.5 The TAU Medical Director may delegate selected aspects of these responsibilities to a physician or resident colleague with sufficient expertise/experience provided that the TAU Medical Director is contactable if needed for consultation.

B.7.2.5.1 The Delegate shall have the following qualifications:

B.7.2.5.1.1 Medical license to practice;

B.7.2.5.1.2 Certification of higher specialist training in Hematology/Transfusion Medicine/Nephrology or other medical specialization ;and

B.7.2.5.1.3 Eight to 12 months of experience in a TAU.

B.7.3 MEDICAL STAFF

B.7.3.1 Medical staffing shall be adequate to meet workload demands and related TAU activities;

B.7.3.2 TAU physicians shall have supervised at least 10 TA procedures (including at least 5 plasma exchange procedures) and they shall have, at least, 3 months of experience in a TAU;

B.7.3.3 Medical personnel shall participate regularly in scholarly/educational activities related to the field of TA as described in the section “Personnel Management”. Such activities should include risk management and patient safety aspects to them.

B.7.4 NURSING STAFF

B.7.4.1 TAU NURSING STAFF shall be adequate to meet workload demands and related activities as identified in these Standards. At a minimum, nurse staffing should be one nurse per two beds;

B.7.4.2 Nursing staff shall have performed at least 10 TA procedures;

B.7.4.3 Nursing personnel shall participate regularly in educational activities related to the field of TA as described in the section “Personnel Management”.

B.7.5 TECHNICAL STAFF

B.7.5.1 Technical Staff must be trained in the use and maintenance of apheresis devices and have performed at least 10 TA procedures, where applicable.

B.7.5.2 Technical personnel shall participate regularly in educational activities related to the field of TA as described in the section “Personnel Management.”

B.7.6 QUALITY MANAGER SUPERVISOR

B.7.6.1 The TAU shall have a QMS (quality manager supervisor) with an adequate experience in TA procedures and in quality management.

B.7.6.2 The Apheresis Collection Facility Quality Manager shall participate in a minimum of ten (10) hours of educational activities related to cellular therapy, cell collection, and quality management annually

B.7.6.3 The QMS shall:

B.7.6.3.1 Manage critical registration of TA procedures;

B.7.6.3.2 Oversee maintenance of patient data registration;

B.7.6.3.3 Manage maintenance of paper copy documentation;

B.7.6.3.4 Manage, if applicable, electronic records and system back up and updating;

B.7.6.3.5 Oversee management of the document control system;

B.7.6.3.6 Oversee and coordinate compliance with all regulatory and accreditation standards and applicable laws;

B.7.6.3.7 Review registration data and clinical outcomes data to improve the quality of care provided by the TAU.

B.8 PERSONNEL TRAINING AND COMPETENCY ASSESSMENT

B.8.1 INITIAL QUALIFICATION OF NEW PERSONNEL

B.8.1.1 The TAU shall have detailed procedures for initial training of new personnel with regard to timing and competency assessment.

B.8.1.2 For initial training, a tutor (with at least 2 years of TA experience) shall manage the training plan (Note: Training plan must be specifically defined, written and approved in a pre-existing SOP) of new personnel, step by step together with the in-charge nurse/technician or TAU Medical Director, if applicable.

B.8.1.3 At the end of initial training period the competency of new personnel shall be reviewed and approved by the TAU Medical Director.

B.8.2 ACTIVE PERSONNEL

B.8.2.1 A job description shall be produced for each TA operator and, if applicable, for each key position (nurses, laboratory technicians, perfusionists) with regard to their specific competencies and roles.

B.8.2.2 The TAU shall have a procedure to describe and document the continuous training and need for retraining of personnel, with regard to its timing and elements to be assessed.

B.8.2.3 Retraining should include internal courses, workshops, meetings, and conferences held by AM specialists.

B.8.2.4 Continued competency shall be assessed at least annually and documented in an evaluation report.

B.8.2.5 Competency assessment shall consider the knowledge of:

B.8.2.5.1.1.1 technical procedures

B.8.2.5.1.1.2 quality system metrics focused on patient safety and risk management

B.8.2.5.1.1.3 applicative skillsets either acquired or improved since the individual's last assessment review.

B.8.2.6 For individuals absent from clinical TAU activities for more than a six month interval, a retraining period shall be established and retraining performed before reentry of that individual into active service.

B.8.2.7 TA Personnel (medical staff and nurses; technicians and perfusionists in services where they are involved in the TAU) shall be trained in first aid measures (e.g., BLS-D Basic Life Support, Early Defibrillation) according to institutional guidelines.

C. PART C: QUALITY SYSTEM

C.1 AIM AND FEATURES OF QUALITY SYSTEM MANAGEMENT

C.1.1 The TAU shall have a controlled quality management system to:

C.1.1.1 Ensure compliance of procedures with rules and regulations in force;

C.1.1.2 Produce validated SOPs to describe actions to be taken in cases of errors, accidents, adverse events;

C.1.1.3 Predict corrective actions, where necessary, to be in compliance with policy, procedures, laws and regulations;

C.1.1.4 Monitor and calibrate periodically TAU equipments and manage the expiration date calendar (daily/monthly, annually).

C.1.2 RAQ (from here onward defined as QMS), or a trained delegate, shall supervise document management.

C.1.3 The TAU Medical Director is overall responsible for Quality System management.

C.1.4 Selected related duties or parts thereof may be delegated to an individual knowledgeable in quality improvement activities who reports to the TAU Medical Director.

C.1.5 The TAU shall have a quality management system that includes at least:

C.1.5.1 Quality Manual;

C.1.5.2 Standard Operating Procedures;

C.1.5.3 Work Instructions;

C.1.5.4 Training Manual;

C.1.5.5 Patient Medical Record.

C.2 QUALITY MANUAL

C.2.1 The TAU shall have a QM (Quality Manual) or QMP (Quality Management Plan) that includes the following information:

C.2.1.1 TAU organizational chart;

C.2.1.2 Description of personnel initial training, continuous training , retraining and competency assessments;

C.2.1.3 List of agreements with third party vendors, suppliers, consultants;

C.2.1.4 Expected results;

C.2.1.5 Description of auditing of the service;

C.2.1.6 Description of error, accident, adverse events reporting and management;

C.2.1.7 Description of emergency and complications management;

C.2.1.8 Description of registration and record keeping;

C.3 MINIMAL PROCEDURES

C.3.1 The TAU shall have a system to manage registrations, forms, standard operative procedures and policies in a clear and efficient way. In particular, there shall be at a minimum policies and procedures addressing the following:

C.3.1.1 Patient admission to the TAU and patient management ;

C.3.1.2 Informed consent management ;

C.3.1.3 Confidential data management;

C.3.1.4 Patient transportation;

C.3.1.5 Biological product management (if applicable);

C.3.1.6 Biological product deviation management (if applicable);

C.3.1.7 Labeling ;

C.3.1.8 TA medical records management;

C.3.1.9 Therapeutic apheresis procedures;

C.3.1.10 Emergency and complications management;

C.3.1.11 Document management system;

C.3.1.12 Quality management and improvement;

C.3.1.13 Error, accident and adverse events management ;

C.3.1.14 Corrective action;

C.3.1.15 Personnel training;

C.3.1.16 Competency assessment;

C.3.1.17 Indicators analysis;

C.3.1.18 Audit;

C.3.1.19 Management and maintenance of instruments and equipment ;

C.3.1.20 Rooms management ;

C.3.1.21 Customer satisfaction ;

C.3.1.22 Management of disposal;

C.3.1.23 Products and reagents management.

C.3.1.24 Risk assessment

C.3.2 Procedures must be clear and understandable to the operators.

C.3.3 A document control procedure must be established providing the history of document reviews and changes and to ensure that only up-to-date versions of documents are in use.

C.3.4 The center shall establish standard formats for documentation, including procedures, worksheets, reports and forms.

C.3.5 A procedure unique identification system must be defined.

C.3.6 All documents must be checked at regular intervals and verified as conforming to the current standard.

C.3.7 All modifications to documents shall be verified, approved, documented and edited by authorized personnel.

C.4 MANAGEMENT REVIEW AND RECORDS

C.4.1 Annually, the TAU director and the QMS shall review the TAU quality system state of the service report.

C.4.2 A report shall be prepared that describes at a minimum the following activities:

C.4.2.1 Organizational, documental, structural changes that have occurred during the past year;

C.4.2.2 Audits performed;

C.4.2.3 The number and types of complaints received and any corrective actions taken;

C.4.2.4 Errors, accidents and deviations from SOPs that have occurred, summary of the investigations, and corrective actions introduced

C.4.2.5 Corrective and preventive actions applied;

C.4.2.6 Adverse events occurrences;

C.4.2.7 Review of personnel training and competence assessments performed;

C.4.2.8 Evaluation of indicators trend (cf. annex I);and

C.4.2.9 Planned activities for the following year.

C.4.3 The TAU Medical Director and QMS shall share and discuss the Annual Management Review report with all TAU personnel after its completion on an annual basis.

C.5 QUALITY RECORDS

C.5.1 The TAU shall ensure that all activities are adequately recorded;

C.5.2 The TAU shall have procedures describing how recording, documentation, and storage of data and registrations are performed;

C.5.3 The TAU shall have a procedure to ensure the traceability of the clinical activities of each patient;

C.5.4 Emergency or high risk situations shall be appropriately registered, documented and communicated to all pertinent parties.

C.5.5 Records shall be accurate, legible, and indelible. The TAU may use paper copies of the records, microfilm or a validated system for electronic data recording for archival storage.

C.5.6 All registrations, row data included, considered as critical for patient safety and privacy shall be maintained for at least 10 years after the clinical use.

C.5.7 Access to documentation and sensitive data shall be limited to authorized subjects and appropriate authorities as defined in written procedure.

C.6 ERRORS, ACCIDENTS AND ADVERSE EVENTS (EAAE)

C.6.1 The TAU shall have a SOP to identify and register errors, accidents and adverse events.

C.6.1.1 The SOP must describe the ways for pertinent party notifications (e.g., EAAE, TAU personnel and appropriate regulatory authorities and the expected timelines for such notifications.

C.6.2 The TAU shall define a process to apply corrective and preventive actions, verify their application, and document their outcomes.

C.7 QUALITY ANALYSIS

C.7.1 A SOP shall be defined to describe the way to periodically analyze and check activities to monitor the efficiency of the TAU.

C.7.2 This procedure shall include details and timing of pertinent audits.

C.7.3 Audits shall be performed by qualified personnel to verify compliance with approved protocols and legal requirements.

C.7.4 Audits shall include at a minimum:

C.7.4.1 Annual audit of documentation of interim assessment of donor suitability and eligibility prior to the start of the collection procedure.

C.7.4.2 Annual audit of documentation of donor eligibility determination prior to start of the collection procedure

C.7.4.3 Annual audit of management of cellular therapy products with positive microbial culture results

C.7.4.4 Annual audit of documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

C.7.5 Results and corrective action plans introduced shall be documented.

C.7.6 Deviations from required security quality parameters shall be accurately analyzed and documented.

C.7.7 Possible corrective and preventive actions introduced shall be included.

C.7.8 Corrective action plans shall be documented, introduced and closed in a complete and efficient manner. Efficiency of preventive and corrective actions introduced shall be evaluated after introduction.

C.8 CUSTOMER (PATIENT/CLINICAL UNIT) SATISFACTION

C.8.1 The TAU shall have a procedure to describe the monitoring and evaluation of the efficiency of its activity from its customers.

C.8.2 The TAU shall describe the way to accept and register complaints from customers/ third parties.

C.8.3 Documents related to customer satisfaction (complaint forms, letters of recommendation, services evaluation questionnaires, etc) shall be reviewed and acted upon accordingly at least annually.

D. PART D: THERAPEUTICAL APHERESIS REQUIREMENTS

D.1 ADMISSION OF THE PATIENT TO THE TAU

D.1.1 The TAU shall define a SOP describing the admission of the patient into its service that includes the following:

D.1.1.1 Evaluation of TA request and its pertinence;

D.1.1.2 Patient acceptance/ rejection criteria;

D.1.1.3 Patient communication and information;

D.1.1.4 Evaluation visit and treatment planning management (TAU outpatient procedures , TAU inpatient procedures, other care areas bed side procedures);

D.1.1.5 Evaluation and planning of venous access placement and management ;

D.1.1.6 Biological risk evaluation and management of infected patients;

D.1.1.7 Informed consent management (see also part D);

D.1.1.8 Patient discharge instructions and follow up visit information.

D.2 INFORMED CONSENT MANAGEMENT

D.2.1 The TAU shall describe in a SOP how informed consent is administered with regard to room where it will be administered to patients and international laws and regulations.

D.2.1.1 All the procedures shall be performed by the TAU team after the acceptance of informed consent by patient; informed consent shall be administered and documented by a qualified health care professional.

D.2.1.2 Informed consent shall describe the TA procedure in detail, in a language clearly understandable to the patient;

D.2.1.3 It shall include information about risks and benefits of the apheretic treatment and related procedures.

D.2.1.4 In the case of foreign patients the presence of a cultural mediator shall be considered;

D.2.1.5 Patients shall have the opportunity to ask questions and they shall be informed about the possibility for their withdrawal/revocation of consent at any time.

D.2.1.6 Informed consent shall be accepted and signed by the patient and witnessed by a qualified health care professional, before starting the TA procedure.

D.2.1.7 In the case of a minor patient, informed consent shall be obtained from both parents or from the legal representative.

D.3 PRIVACY MANAGEMENT

D.3.1 The TAU shall establish a policy for the use, management, storage and sharing of confidential personal information and data.

D.3.2 The policy shall comply with applicable laws and regulations.

D.3.3 The patient shall be informed about the data management policy by the TAU and shall authorize the use of such data and information by the TAU.

D.3.4 The patient's consent to such processes will be documented.

D.4 PATIENT TRANSPORTATION

D.4.1 The TAU shall have a SOP to describe the timing and characteristics of transportation of hospitalized patients (i.e., inpatients) and patients receiving TA on an outpatient basis to and from the TAU.

D.4.2 Transport shall be conducted in the safest way for patient and operators.

D.4.3 Transportation shall be carried out by qualified and authorized personnel.

D.5 BIOLOGICAL PRODUCT MANAGEMENT

D.5.1 For biological product management the TAU shall describe:

D.5.1.1 Procedures for receiving biological products, their labeling and product(s) traceability;

D.5.1.2 Acceptance criteria endpoints and quality control performance measures will be defined, documented and periodically audited;

D.5.1.3 Biological product deviations management with respect to described endpoints and QC performances measures will be defined; and

D.5.1.4 A procedure for the discarding of apheresis products will be defined.

Offline products follow all the previous points; online products follow points D5.1.2 e .3

D.5.2 OFFLINE PRODUCTS

D.5.2.1 The TAU shall define acceptance, management and release procedures for offline products preferably by using non-manual transcription processes. Procedures shall describe at least the following:

D.5.2.1.1 Product acceptance criteria and coding by qualified informed systems, that comply with UNI 10529 standards and subsequent updates;

D.5.2.1.2 Identification using qualified labels, directly produced by a label management system providing unique identification numbers with validation by a double-check attestation process performed by qualified personnel;

D.5.2.1.3 The history of product acquisition and its subsequent treatment/processing clearly described on the label or in an attached form;

D.5.2.1.4 Product release criteria and reinfusion parameters with documentation of qualified operator/s involved and criteria for clear and safe recipient/product identifications;

D.5.2.1.5 Methods of reinfusion;and

D.5.2.1.6 Traceability of all elements in the entire process.

D.5.3 PRODUCT QUALIFICATION CRITERIA AND QUALITY CONTROL

D.5.3.1 Products obtained by online and offline procedures shall comply with qualifications parameters described in the specific SOP and with the national regulations. Evidence shall be shown by documentation of the use of pertinent controls that shall include at least the following:

D.5.3.1.1 Control frequency; and

D.5.3.1.2 Qualification parameters defined by historical or scientifically validated controls.

D.5.3.2 An examination of product management data shall be performed and documented in the annual service review report by the executive leadership of the TAU.

D.5.4 PRODUCT DEVIATIONS MANAGEMENT

D.5.4.1 The TAU shall describe a procedure to define product deviations management, including at least the following:

D.5.4.1.1 A list of recognized unacceptable deviations and causes;

D.5.4.1.2 Management of acceptable/known causes and clinical decisions agreed upon by all pertinent parties regarding the clinical use and reinfusion of any such products;

D.5.4.1.3 Release and exceptional release criteria and deviations;

D.5.4.1.4 Product deviations management resulting in an unexpected non-compliance situation; and

D.5.4.1.5 In cases of non-compliance, the performance of outcome analysis audits after resolution of the event.

D.6 CASE HISTORY MANAGEMENT

D.6.1 The TAU shall define a SOP to describe registration, management, and the acquisition of patient and performed procedures data and information; including data regarding adverse events and reactions occurrences.

D.6.1.1 The SOP will also define how such data and information will be documented and filed.

D.6.2 The TAU Medical Director is responsible for the overall oversight of the clinical Case History Management process.

D.6.3 The TAU case history shall include at a minimum the following:

D.6.3.1 Anamnestic data regarding patient and the major aims of the proposed TA therapy;

D.6.3.2 Diagnostic/ instrumental examinations of the patient;

D.6.3.3 Diagnosis and pertinent problems list;

D.6.3.4 Clinical documentation and diagnostic analysis to evaluate patient eligibility for the clinical treatment and/or any possible treatment deviations;

D.6.3.5 Registration of procedure data and traceability of the team that performed the procedure;

D.6.3.6 Notification of adverse event/reactions;

D.6.3.7 Formulation of the pertinent therapeutic plan;

D.6.3.8 Informed consent for the apheretic procedure; and

D.6.3.9 Registration of infusional or pharmacological treatments performed during the peri-apheresis period (i.e., pre-, intra-, post-procedure).

D.6.4 The TAU shall define the location where case histories are filed.

D.7 THERAPEUTIC APHERESIS PROCEDURE

D.7.1 The TAU shall describe the process of Therapeutic Apheresis in a procedure that includes at least the following:

D.7.1.1 Documentation of operative instructions and elements pertinent to the apheretic procedure, including materials used and their lot identification numbers and expiration dates; assembly / disassembly of device circuits, and priming step, startup, reinfusion parameters;

D.7.1.2 Planning and management for apheretic technology to be used;

D.7.1.3 Central venous catheter placement and management;

D.7.1.4 Replacement fluid management;

D.7.1.5 Early cessation of the procedure and expected procedure deviations management; and

D.7.1.6 Operative procedure data documentation and management.

D.8 PEDIATRIC-RELATED ASPECTS

D.8.1 A pediatric TAU must staffed by individuals with specific expertise and experience pertinent to the care and management of pediatric patients.

D.8.2 The pediatric TAU room shall be designed to account for the comfort of children and parents.

Special attention must be paid to maintenance of the child's cooperation.

D.8.3 The Pediatric TAU shall describe a procedure for maintenance of a constant intravascular volume during apheretic procedures.

D.8.4 The extracorporeal volume displacement should not exceed 15% of the total blood volume of the patient.

D.8.5 The Pediatric TAU shall describe operative instructions for the management of apheresis device circuit priming with leukodepleted /filtered and irradiated red cells for low weight patients and/ or all patients with anemia, unstable blood pressures or signs and symptoms of hypovolemia.

D.8.6 The Pediatric TAU shall describe a procedure for the management of venous access including a policy for choosing the appropriate size of the CVC to be used.

D.8.7 The Pediatric TAU shall describe a protocol to avoid complications of anticoagulation;

D.8.8 Ionized calcium levels should be tested every 60 minutes.

D.8.9 All materials shall be suitable and validated for pediatric use

D.9 EMERGENCY AND COMPLICATIONS MANAGEMENT

D.9.1 The TAU shall describe a procedure for the management of emergency/adverse events that may potentially occur during TA.

D.9.2 The TAU personnel shall be adequately informed, instructed and periodically updated on the management of urgent/emergent events/adverse complications/accidents that can occur during TA.

D.9.3 The TAU shall define a plan for the immediate availability of drugs, medical devices, and support personnel (e.g., Rapid Response Teams) to ensure the highest levels of safety for patients including support involving cardiac resuscitation.

D.9.4 To ensure the highest levels of safety for personnel and patients, the TAU shall document periodic auditing and compliance with the following:

D.9.4.1 Alarm management;

D.9.4.2 Types of complications and management;

D.9.4.3 Clinical interventions requiring the involvement of intensive care personnel.

D.9.5 The TAU shall have a SOP that:

D.9.5.1 Defines responsibilities and extent of monitoring/care of the patient by the TAU staff during the peri-apheresis interval including the post apheresis time interval until the next scheduled TA; and

D.9.5.2 Defines potential accidents related to materials, devices and equipment used during the TA procedure and the corrective actions needed to be introduced for a rapid intervention and resolution of problems.

D.10 DISPOSAL MANAGEMENT

D.10.1 The TAU shall define a SOP regarding medical waste management and disposal which describes collection, transportation, and disposal with respect to the environment.

D.10.2 The TAU shall define emergency procedures for sanitization and decontamination in the cases of accidental contamination by hazardous materials.

D.11 CRITICAL MEDICAL DEVICES AND EQUIPMENT MANAGEMENT

D.11.1 All materials considered as critical for patient care shall be validated according to the manufacturers' guidance (i.e., technical specifications). These materials

must be supplied by industries that have obtained a CE mark for devices and disposables or an FDA approval. In any case, all apheresis equipments must have evidences of a clear and consolidated procedure efficacy and safety as reported in available scientific sectorial literature. Not-referenced equipments in published literature must be validated and used in a declared and formalized experimental context.

D.11.2 The TAU shall produce a list of all critical materials (at least apheresis kits, labels, detergents, medications, etc) and document their process of validation.

D.11.3 Manuals, instruction forms, technical sheets, and any documentation materials pertinent to the reliability and qualification of these materials shall be maintained in the TAU.

D.11.4 The TAU shall have a SOP describing supply, management, identification, qualification, control, and storage processes of all critical materials listed. This SOP shall indicate specific responsibilities regarding the charge /discharge of materials and the expiry date management of the items.

D.11.5 The SOP shall also describe:

D.11.5.1 Minimum stock levels for each product; and

D.11.5.2 A plan for the periodical monitoring (at least monthly) of their expiration.

D.11.6 The TAU shall define a policy for the isolation of non-compliant or aberrant products and how to notify pertinent authorities and vendors regarding the possible use of these products.

D.11.7 All critical materials shall be stored in areas, rooms, and devices appropriate to prevent quality alterations to the items.

D.12 RECORD KEEPING

D.12.1 GENERAL

D.12.1.1 The TAU shall have written procedures for record keeping and management.

D.12.1.2 All records shall be clear, readable and indelible.

D.12.1.3 All documentation shall be stored in dedicated areas; if documentation is stored in different areas, the TAU shall provide a system to ensure immediate and unambiguous identification of pertinent records.

D.12.1.4 Documentation shall be stored with respect to privacy and safety laws and regulations in force.

D.12.1.5 Records shall be labeled using an organized system and a list of contents shall be produced to easily identify pertinent items.

D.12.2 MANAGEMENT OF HARDCOPY ARCHIVES

D.12.2.1 Documentation shall be kept in order to ensure the ability for adequate checks and interpretations during an audit.

D.12.2.2 The places in which the documentation are archived shall have:

D.12.2.2.1 Glass shields (if applicable);

D.12.2.2.2 Controlled access; and

D.12.2.2.3 Fire protection/suppression systems.

D.12.2.3 A Case History shall be archived for 30 years.

D.12.3 ELECTRONIC FILING OF DOCUMENTS

D.12.3.1 Documents archived by means of an electronic system should have:

D.12.3.1.1 Validation prior to first use; and

D.12.3.1.2 Documentation of such validation.

D.12.3.2 Electronic filings shall comply with privacy and safety laws and regulations.

D.12.3.3 Protection of data integrity, authenticity and traceability shall be ensured.

D.12.3.4 The TAU shall define a system to ensure the access to electronic data only to authorized personnel.

D.12.3.5 All changes to the system shall be authorized, documented and validated, and in all cases approved by the Medical Director of the TAU.

D.12.4 BACK UP AND SECURITY OF ELECTRONIC SYSTEM

D.12.4.1 The TAU shall have a backup system to allow for the recovery and maintenance of all TA documentation.

D.12.4.2 The TAU shall have emergency procedures in cases of accidents to retrieve entire aspects of documentation.

D.12.4.3 Documents shall be periodically verified and filed into an alternative electronic system that is compliant and non-perishable.

E. PART E: OUTCOMES AND INDICATORS

E.1 OUTCOMES

E.1.1 The TAU shall define efficiency evaluation criteria for treatments performed with monitoring of the progress achieved annually.

E.1.2 The TAU shall, at a minimum, periodically monitor the frequency with which patients' treatments must be stopped for ineffectiveness.

E.2 INDICATORS

E.2.1 TAU shall ensure the continuous monitoring of its activity by documenting the following:

E.2.1.1 Progress of activities;

E.2.1.2 Achievement of the objectives set out; and

E.2.1.3 Continuous quality improvement.

E.2.2 The TAU Medical Director, together with the QMS, shall review the indicators and they shall share the results with all TAU personnel annually.

F. PART F: APPLICATION OF TAU STANDARDS IN JACIE/FACT-ACCREDITED HPC COLLECTION UNITS ALSO INVOLVED IN GENERAL THERAPEUTIC APHERESIS

In those cases in which the TAU standards will be applied and verified in a unit where JACIE/FACT-accredited activities are also performed together with other apheretic procedures that have been successfully subjected to the quality system assurance provided by JACIE/FACT itself, the application of the present standard will carefully verify the following evidences:

F.1 Evidence of effective implementation of a general system for quality assurance according to JACIE/FACT rules for all apheretic procedures, including HPC, APHERESIS collection procedures;

F.2 The competency and training of all TAU staff, including the TAU Medical Director according to the rules of the present standards and minimal required volume activity /year levels for accreditation as identified by these TAU Standards;

F.3 The biological product management for non HPC, APHERESIS collection procedures, according to these TAU Standards;

F.4 The existence of dedicated procedures to manage relevant issues in pediatric apheresis (D.8) if applicable to the TAU; and

F.5 The full application of all mandatory indicators, including those specifically created for HPC, APHERESIS collection procedures (See Annex1).

ANNEX I:

a) Table of Procedures and Outcome Indicators. The following indicators are intended as: Yellow: Recommended Indicators; Green: Mandatory Indicators

Indicators	Obligatories		Monitored Activity
Indicators for therapeutic procedure demand and availability	Recommended	Mandatory	
Number of bed-side procedures by TAU/ number of total procedures performed	Recommended		Extramural activity
Number of emergency procedures by TAU/number of total procedures performed	Recommended		Emergency activity
Time from procedure initial consultation to the start of the first therapeutic session	Recommended		Organizing efficiency
Resource indicators	Obligatories		Monitored Activity
TAU total procedures/TAU physicians	Recommended		Workload recording/ personnel appropriateness
TAU total procedures/TAU nurses and technicians	Recommended		Workload recording/ personnel appropriateness
Total TAU procedures/number of TAU apheresis devices	Recommended		Rate of apheresis devices utilization
Activity indicators	Obligatories		Monitored Activity
Number of TAU total procedures/number of procedures required by the standard	Mandatory		Standards implementation
Number of TAU procedures / physician / year	Mandatory		Standards implementation
Number of TAU procedures/ nurse-technician / year	Mandatory		Standards implementation
Outcomes indicators	Obligatories		Monitored Activity
Percent annual variations of insertion of venous catheters (number of patients with an inserted catheters/total number of patients)	Mandatory		Evaluation of modalities for vascular accesses
Number of moderate-severe adverse reactions/number of total procedures	Mandatory		Clinical risk assessment
Number of delivered satisfaction questionnaires to customers/number of questionnaires given back by customers	Mandatory		Customer satisfaction
Number of complaints per year	Recommended		Customer satisfaction
Number of patients with ASFA category I, II, III designations/total number of patients(index stratified for a single category or aggregated for all categories)	Mandatory		Clinical appropriateness
Number of patients with efficacious /inefficacious apheretic course / total number of patients	Mandatory		Clinical outcomes
Number of interrupted procedures /total number of procedures (for patients' complications)	Mandatory		Processes for patients' apheretic care
Number of interrupted procedures /total number of procedures (for procedure complications/malfunctioning)	Mandatory		Machine and alarm management
Number of total adverse events/ number of total procedures	Mandatory		Quality improvement

Annex I:
b) Specific outcome indicators for apheretic activities included in the JACIE accreditation area

The following indicators are intended as:
Yellow: Recommended Indicators; Green: Mandatory Indicators

Outcome Indicators	Obligatories	Monitored Activity
Number of collection procedures to obtain an autologous graft	Mandatory	Apheretic efficacy
Number of collection procedures to obtain an allogeneic graft	Mandatory	Apheretic efficacy
Average number of CD34+ cells/ml immediately before patients' first HPC collection	Mandatory	Timing Appropriateness
Average number of CD34+ cells/ml immediately before donors' first HPC collection	Mandatory	Timing Appropriateness
Percent of patients requiring adjunctive mobilization (e.g., Plerixafor addition)	Mandatory	Appropriateness
Average patients' blood volume processed per HPC procedure (expressed as ml/kg) if applicable (in cases of LVLs)	Recommended	Methodological appropriateness
Average donors' blood volume processed per HPC procedure (expressed as ml/kg of recipient) if applicable (in cases of LVLs)	Recommended	Methodological appropriateness
Ratio CD34+ cell measured/predicted yield in cases of prediction methods	Recommended	Methodological appropriateness
Average percent collection efficiency of autologous HPC collections	Mandatory	Efficiency
Average percent collection efficiency of allogeneic HPC collections	Mandatory	Efficiency

Outcome Indicators	Obligatories	Monitored Activity
Average number of granulocytes (PMN) in autologous HPC collections expressed as PMN x 10^9 for each single apheretic procedure	Recommended	Procedure selectivity
Average volume of RBC (expressed in ml) contaminating each autologous HPC collection	Recommended	Procedure selectivity
Average volume of RBC (expressed in ml) contaminating each allogeneic HPC collection in case of major ABO mis-match	Recommended	Procedure selectivity
Number of Collected Products positive in microbiological testing post collection	Mandatory	Safety