International Standard for

Therapeutic Apheresis Unit

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INTRODUCTION

Therapeutic Apheresis 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 our country about 14,000 annual plasma-exchange treatments, using therapeutic apheresis procedures, and approximately 7,000-8,000 photopheresis/extracorporeal photochemotherapy procedures are performed per year, the latter in graft versus host disease, for prevention or treatment of organ solid rejection, in auto-aggressive rapidly evolving diseases or dependent by immunosuppressants, and in cutaneous T-cell lymphomas. Therefore, there is a high rate of application of these forms of treatment with a frequency that, when compared to the Italian population, approximates to about 1 therapeutic apheresis procedure per year every 2,900 residents. A frequency of this order, if reported on an European scale, could suggest a number of procedures per year of approximately 170,000 treatments in all European countries. Although recalibrated in the different levels of technological advancement of the various countries, the number could approach approximately 100,000 procedures per year. As already mentioned, these therapeutic procedures are characterized as a series of treatments of high complexity that requires an appropriate technological skills and medical expertise, grown up in suitable and documented fashion, as well as dedicated facilities with organizational structures able to ensure operational efficacy and efficiency. Specific skill and requirements in this field need to be carefully combined with the current knowledge regarding the therapeutic indications of therapeutic hemapheresis, periodically updated by American Society for Apheresis (ASFA) on its official organ Journal of Clinical Apheresis, in an organizing model that allows the best exploitation of existing knowledge and technology and to ensure safety, effectiveness, and efficiency of these therapeutic procedures, in a continuous process of quality improvement. In other words, modern organizing models and systems for quality implementation and quality permanent observance, must identify a reference "standard" for therapeutic apheresis, in the same way as the international standard JACIE-FACT has been created and applied for collection and clinical use of hematopoietic stem cells for transplantation. In this context, the Società Italiana di Emaferesi e Manipolazione Cellulare (SIdEM), in collaboration with the sector company Exem Consulting, has created a standard for Therapeutic Apheresis (Standard TAU, Therapeutic Apheresis Unit) that may translate into a national organizing and quality model and, in the near future, into an European operational reference for the continuous improvement of this therapeutic area. This standard has been created by a team of professionals and experts with the sole aim of identifying all the required information to ensure that centers involved in Therapeutic Apheresis may follow uniform and traceable operational guidelines. The standard TAU wants to be an operational tool that allows, in all centers of therapeutic apheresis, the introduction of a full-quality organizing model which may also, if appropriate, integrate and complete partial organizing models already spontaneously adopted.

Therefore, the standard TAU is proposed to define organizing requirements, procedures, and a general management strategy that all therapeutic apheresis centers should follow to
set up an appropriate system of quality assurance, consistently monitored, observed and implemented.

The implementation of this standard ensures consistency in the management of patients, in the set up of procedures, and rules for the proper recording of performed activities, based on functioning and quality requirements shared at national and international level. The standard TAU was designed to define the minimum required organizing guidelines for centers of therapeutic apheresis and not intended to replace any regulations, laws, and national and international regulations in force in the country in which it will be applied. The goal of each TAU center which will implement the standard is that of a fine and permanent analysis of its activities at procedural and organizational level and that to define proper processes through which its own activities may be rendered fully compliant.
A. PART A: TERMINOLOGY AND ABBREVIATIONS, DEFINITIONS

A.1 TERMINOLOGY AND ABBREVIATIONS

TAU: Unit of Therapeutic Apheresis
RAQ: Quality Manager
QMS : Quality Manager Supervisor
TA: Therapeutic apheresis
IT: Immunotrasfusional Unit
SOP: Standard Operating Procedures
BMT: Bone Marrow / Hematopoietic Precursors Transplant
PTT: Thrombotic Thrombocytopenia Purpura
PPE: Personal Protective Equipment
AREA: the area not bounded (which is part of a room)
ROOM: Enclosed Area With Controlled Access
EQUIPMENT: all technological equipment in use at TAU, whose operation leads to a critical impact on the health of the patient
MATERIALS: all products, reagents, drugs, kits, liquids that are used in the TAU for the realization of the service
CVC: Central Venous Catheter

A.2 DEFINITIONS

Biological products: products generated by a process of therapeutic apheresis processed / manipulated / treated, before being assigned to a direct reinfusion to the patient

Online product: product obtained by an apheretic procedure without detachment from the collection circuit and subsequent treatment (eg: photopheresis)

Offline product: product obtained by an apheretic procedure with detachment from the collection circuit and subsequent treatment (eg: Extracorporeal photochemotherapy)

Critical: all procedures, products, reagents, kits, whose deviations cause a danger for patients or personnel. They must be periodically validated
B. Part B: TAU GENERAL REQUIREMENTS

B.1 TAU ORGANIZATION

B.1.1 TAU personnel consists of a medical, nurse and, if applicable, technical team coordinated by a medical director.

B.1.1.1 A TAU shall perform the following procedures:
- Therapeutic Cytoapheresis
- Plasma/Red Cell Exchange
- Hemo/Plasma treatment
- Photopheresis/Extracorporeal Photochemotherapy

B.1.2 TAU shall abide by all applicable law and regulations.

B.1.3 TAU shall abide by FACT-JACIE standard to perform apheretic procedures for BMT.

B.1.4 To be accredited, according to TAU standard, each TAU shall perform, at least, 100 TA procedures or at least 100 apheresis procedures with no less than 50 TAs, if also productive apheresis on patients (i.e. HPC collection) were performed.

B.1.5 To be accredited a TAU performing procedures for pathologies in which AT is an emerging and mandatory treatment (i.e.: PTT, acute chest syndrome in drepanocytosis, Leukemic hyperleukocytosis with Leukostasis, hyperviscosity syndrome clinically expressed) must guarantee 24-hour 7 day/week activity.

B.2 FACILITY REQUIREMENTS

B.2.1 TAU shall have appropriate rooms and areas to perform all the therapeutic activities to:

B.2.1.1 Comply with safety requirements for patients and personnel
B.2.1.2 Protect patient privacy
B.2.1.3 Avoid any risk of error or cross contamination
B.2.1.4 Allow easy cleaning, sanitization and ordinary or extraordinary maintenance of rooms and instruments
B.2.1.5 The following shall be ensured:

B.2.1.6 Room suitability before use, after periodical maintenance control or after introducing relevant changes.

B.2.2 Maintenance of appropriate Humidity, Temperature and ventilation conditions/features must be guaranteed in an appropriate SOP.
B.2.3 TAU shall have space and locations adequate to number and type of procedures performed

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

B.2.5 TAU shall have, at minimum, the following areas and locations:
   B.2.5.1 Patient reception and registration area
   B.2.5.2 A designated area for patient care in compliance with privacy requirements, for medication, medical visit or confidential evaluation
   B.2.5.3 Rooms or areas adequate to administrate therapeutic treatment with, at least, two beds/chairs and a pediatric area, when appropriate
   B.2.5.4 Cleaning services separated for patients and personnel
   B.2.5.5 A storage area for materials and first use drugs
   B.2.5.6 An appropriate area for preparation of replacement solution and for manipulation of apheretic products for rapid reinfusion in compliance with requirements of sterility
   B.2.5.7 A storage area for rapid and recent use documents and records.
   B.2.5.8 An appropriate area for discard of apheretic products/materials

B.2.6 TAU shall have written procedures for rooms cleaning, sanitization and maintenance management

B.2.7 TAU shall define emergency action to be taken in case of chemical, physical or biological environmental contamination

B.3 SUPPORT SERVICES

B.3.1 TAU shall be included in an Hospital with the following facilities:
   B.3.1.1 Immunohematology laboratory and Transfusion Service
   B.3.1.2 Diagnostic laboratory of clinical chemistry and microbiology

B.3.2 Intensive care and recovery room

B.3.3 TAU shall define procedures and timing of access to support services while performing therapeutic procedures.

B.3.4 In particular, TAU shall define the procedure to rapidly access to intensive care in case of emergency.

B.3.5 If TAU does not have an internal Immunotransfusion service and/or a diagnostic laboratory it shall define an written agreement with an external facility. access procedures and timing shall be validated.
B.4 TAU EQUIPMENT

B.4.1 TAU Equipment shall be adequate to type and number of services provided. A backup separator apheresis machine shall be provided for emergency procedures.

B.4.2 Oxygen devices shall be available at bed/chair position

B.4.3 TAU shall have emergency equipment available provided with emergency drugs and devices and with a dedicated defibrillator or, as an alternative for this last point requiring defibrillator, an immediate access to the emergency team and equipments

B.4.4 TAU shall describe a SOP for management of control, availability, expiration, supply and responsibility of emergency equipment drugs and devices

B.4.5 Conformity of emergency equipment shall be certified.

B.4.6 TAU equipment shall be validated for their intended use; in case of malfunction or extraordinary maintenance equipment shall be re-validated.

B.4.7 Electrical equipment shall have a power supply system that ensures the maintenance of activity even in the absence of electricity supply in the overall network.

B.4.8 TAU shall have a list and maintain records of all critical equipment, in particular:
   B.4.8.1 Instrument location
   B.4.8.2 Handbook location
   B.4.8.3 Instrument access documentation
   B.4.8.4 Review of previous and last instrument maintenance
   B.4.8.5 Entire documentation of instruments activity

B.4.9 Equipment register shall be periodically maintained

B.4.10 TAU shall define a procedure to detect instrument workload and to couple the instrument with the procedure performed.

B.5 TAU SAFETY

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

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

B.5.3 TAU shall have a written procedure, that abide to national laws and requirements, for biohazard waste disposal, to minimize personnel contamination

B.5.4 All Personnel shall wear PPE while performing procedures in TAU
B.6 EXTERNAL AGREEMENTS

B.6.1 TAU shall contract agreements with individuals/external facilities that have a relevant impact for TAU activity (more than 10 procedures per year).

B.6.2 Agreements shall include descriptions of role and responsibility of each part.

B.6.3 Agreements shall be dated and signed by their respective directors and revised at least every two years.

B.6.4 Supplier relationship, that are managed by Administration, are not bound by agreements (eg supply).

B.6.5 TAU shall describe policy or procedures for patient admission and management that shall be shared with requiring department/ward. A referent physician shall be identified to interact with TAU in case of urgent communications.

B.6.6 If an Immunotransfusional Unit is not included in TAU, there shall be an agreement with an external IT (organizational, management of blood products etc..)

B.7 TAU PERSONNEL ORGANIZATION

B.7.1 General

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

- TAU Director
- Medical Staff
- Nursing Staff
- Technical staff
- Quality manager

B.7.1.2 TAU shall describe an organization chart to define personnel roles and responsibilities.

B.7.1.3 TAU shall contract agreement with external facilities to abide by required procedures.

B.7.1.4 Agreements could be contracted with individuals as long as this cannot produce a conflict of interest.

B.7.2 TAU DIRECTOR

B.7.2.1 TAU Director shall have the following minimum requirements:

- Medical License
B.7.2.2 Certification of higher specialist training in Hematology/Transfusion Medicine/Nephrology or other medical specialties and two years of documented experience in TA

B.7.2.2.1 TAU Director shall have the following training:

B.7.2.2.2 He must have supervised, at least 100 apheresis procedures with no less than 50 TAs; if also productive apheresis (i.e. HPC collection) were performed, 100 TA procedures including at least 50 TA procedures with the “100 cutoff” that may be reached by combining productive apheresis procedures and TA on patients (eg. Collection of HPCA) performed during the 12 months prior to accreditation

B.7.2.3 TAU Director is responsible of:

B.7.2.3.1 Clinical procedures, quality management, efficiency of services supplied for patient care during TA procedures (initial evaluation; treatment, complications)

B.7.2.3.2 Personnel Training and evaluation

B.7.2.3.3 All the management TAU procedures

B.7.2.3.4 TAU Quality system maintenance with regard to national and international laws and requirements

B.7.2.4 Management of the interaction between TAU and facility organizers

B.7.2.5 TAU director shall participate regularly in educational activities related to the field of TA (courses, congresses, scientific publications/paper...) to give evidence of continuous training on field

B.7.2.6 TAU director may delegate his responsibilities to a resident deputy with sufficient expertise as long as he can ensure a telephone availability

B.7.2.6.1 Delegate shall have the following qualifications:

B.7.2.6.2 Medical license

B.7.2.7 Certification of higher specialist training in Hematology/Transfusion Medicine/Nephrology or other medical specialization

B.7.2.8 12 months of experience in a TAU

B.7.3 MEDICAL STAFF

B.7.3.1 Medical staff shall be adequate to workload and 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 educational activities related to the field of TA as described in the section “personnel management”

B.7.4 NURSING STAFF

B.7.4.1 TAU NURSING STAFF shall be adequate to workload and activities which TAU standard requires,. At a minimum, 1 nurse per 2 beds

B.7.4.2 Nursing staff shall have, at least, an experience of 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 device and have , at least, an experience of 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 TAU shall have a QMS (quality manager supervisor) with an adequate experience in TA procedures and in quality management

B.7.6.2 QMS shall:

B.7.6.2.1 Manage critical registration of TA procedures

B.7.6.2.2 Guarantee maintenance of patient data registration

B.7.6.2.3 Manage maintenance of hard copy documentation

B.7.6.2.4 Manage, if applicable, electronic records and system back up and updating

B.7.6.2.5 Guarantee management of document control system

B.7.6.2.6 Guarantee that quality system is applied and in compliance with regulations and laws in force.

B.7.6.2.7 Review registration data and clinical outcome to improve quality management system.
B.8 PERSONNEL TRAINING AND COMPETENCY ASSESSMENT

B.8.1 INITIAL QUALIFICATION OF NEW PERSONNEL

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

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

B.8.1.3 At the end of initial training the competency of new personnel shall be guaranteed by TAU director.

B.8.2 ACTIVE PERSONNEL

B.8.2.1 A “current job description” shall be produced for each TA operator and, if applicable, for each key position (nurses, laboratory technicians, perfusionists) with regards to specific competences and roles.

B.8.2.2 TAU shall have a procedure to describe continuous training and retraining of personnel, with regards to continuous competency and retraining assessment timing.

B.8.2.3 Retraining should include internal courses, workshop, meeting, and conferences held by specialists.

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

B.8.2.5 Competency assessment shall consider the knowledge of: technical procedures, quality system and applicative skills acquired or improved.

B.8.2.6 A retraining shall be planned for personnel out of TA unit activity for more than 6 months.

B.8.2.7 TA Personnel (medical staff and nurses; technicians and perfusionists in case they are involved in the TAU) shall be trained for first aid action (BLS-D Basic Life Support, Early Defibrillation), in case of emergency.

C. PART C: QUALITY SYSTEM

C.1 AIM AND FEATURES OF QUALITY SYSTEM MANAGEMENT

C.1.1 TAU shall have a controlled quality 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 taken in case 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 an accurately trained delegate, shall supervise document management

C.1.3 TAU Director, or a delegate with documented experience and training, is responsible for Quality System management

C.1.4 TAU shall have a quality management system that includes at least:

C.1.4.1 quality manual
C.1.4.2 standard operating procedures
C.1.4.3 work instruction
C.1.4.4 training manual
C.1.4.5 patient medical record

C.2 QUALITY MANUAL

C.2.1 TAU shall have a QMP (Quality Management Plan, ) including the following information:

C.2.1.1 TAU organizational chart
C.2.1.2 Personnel initial training, continuous training, retraining and competency assessment
C.2.1.3 Agreement with third parts
C.2.1.4 Expected results
C.2.1.5 Audit
C.2.1.6 Error, accident, adverse event management
C.2.1.7 Emergency and complications management
C.2.1.8 Registration and record keeping

C.3 MINIMAL PROCEDURES

C.3.1 TAU shall have a system to manage registrations, forms, standard operative procedures and policy in a clear and efficient way. In particular, there shall be at a minimum:
C.3.1.1 Patient admission to the TAU and patient management
C.3.1.2 Informed consent management
C.3.1.3 Sensitive 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 system management
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's satisfaction
C.3.1.22 Management of disposal
C.3.1.23 Products and reagents management

C.3.2 Procedures must be clear and understandable to the operators
C.3.3 A document control procedure must be established to provide for the history of document reviews and changes and to ensure that any updated version of documents are in use
C.3.4 The center shall establish standards for the documentation, including procedures, worksheets, reports and forms
C.3.5 A procedure numbering 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, TAU director and QMS shall review the TAU quality system state of art

C.4.2 A document shall be produced that describes at a minimum the following chapters:
   C.4.2.1 Organizational, documental, structural changes occurred during the year
   C.4.2.2 Audit performed report
   C.4.2.3 A Report about the number of complaints
   C.4.2.4 Errors, accidents and deviations from SOPs occurred and corrective actions introduced
   C.4.2.5 Corrective and preventive actions applied
   C.4.2.6 Adverse events occurred
   C.4.2.7 Analysis of personnel training and competence assessment performed
   C.4.2.8 Evaluation of indicators trend (cf. annex I)
      C.4.2.8.1 Aim proposed for the next year

C.4.3 At completion of the document TAU director, medical director and QMS shall share and discuss the Annual Management Review with all the TAU personnel

C.5 QUALITY RECORDS

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

C.5.2 TAU shall have procedure to describe way of recording and storing data and registrations.

C.5.3 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 registered and notified

C.5.5 Records shall be accurate, legible, and indelible. TAU can use hardcopy of the records or it can use a validated system for electronic data recording or a microfilms

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 To ensure confidentiality required, Records shall be in compliance with applicable laws and regulations. Access to documentation and sensitive data shall be limited to authorized subjects and competent authorities as defined by laws.

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

C.6.1 TAU shall have a SOP to identify and register errors, accidents and adverse events. This SOP clearly describe the way to notify EAAE, immediately to TAU referred personnel and to competent authority.

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

C.7 QUALITY ANALYSIS

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

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

C.7.3 Audits shall be performed by qualified personnel to verify compliance with approved protocols and legal requirements. Results and corrective actions introduced shall be documented.

C.7.4 Deviations from security quality parameters required shall be accurately analyzed and documented. Possible corrective and preventive actions introduced shall be included.

C.7.5 Corrective actions 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 TAU shall have a procedure to describe monitoring and evaluation of the efficiency of its activity from customers.

C.8.2 TAU shall describe the way to accept and register complaints from customers/ third parties.
C.8.3 Periodically (at least annually) documents related to customer satisfaction shall be reviewed (complaint forms, letters of recommendation, services evaluation questionnaire...)
D. PART D: THERAPEUTICAL APHERESIS REQUIREMENTS

D.1 TAKE IN CHARGE OF THE PATIENT

D.1.1 TAU shall define a SOP to describe the take in charge of the patient that includes at least:

D.1.1.1 Evaluation of request 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 outpatients, TAU inpatients, bed side…);
D.1.1.5 Evaluation and planning of venous access 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 and follow up.

D.2 INFORMED CONSENT MANAGEMENT

D.2.1 TAU shall describe in a SOP how informed consent is administered with regards 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 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 procedure details, in a language clearly understandable to the patient; it shall include information about risks and benefits of the apheretic treatment and related procedures.
D.2.1.3 In the case of foreign patients the presence of a cultural mediator shall be considered.
D.2.1.4 Patient shall have opportunity to ask questions and they shall be informed about the possibility to withdraw/revoke consent at any time.
D.2.1.5 Informed consent shall be accepted and signed by the patient and a qualified health care professional, before starting procedure.
D.2.1.6 In the case of a minor patient, informed consent shall be obtained by both parents or by a legal tutor.
D.3 PRIVACY MANAGEMENT
D.3.1 TAU shall abide to national and international regulations in the field of sensitive data management
D.3.2 Patient shall be informed about sensitive data management and shall authorize it

D.4 PATIENT TRANSPORTATION
D.4.1 TAU shall have a SOP to describe timing and characteristics of transportation of the patient to and from the TAU center. It shall be conducted in the safest way for patient and operators.
D.4.2 Transportation shall be carried out by qualified and authorized personnel

D.5 BIOLOGICAL PRODUCT MANAGEMENT
D.5.1 For biological product management TAU shall describe:
   D.5.1.1 Procedures for taking charge of biological product, labeling and product traceability
   D.5.1.2 Acceptance endpoints and quality control to perform
   D.5.1.3 Biological product deviations management with respect to described endpoints.
   D.5.1.4 A procedure to discard apheresis products

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 TAU shall define take in charge, management and release procedures for offline products, which could avoid, if applicable, manual transcription step. Procedures shall describe at least:
   D.5.2.1.1 Product acceptance and coding by qualified informed systems, that comply with UNI 10529 standard and following updates
   D.5.2.1.2 Labeling by qualified labels, directly produced by management system with unique identification number, validated by a double check performed by qualified personnel.
D.5.2.1.3 Product treatment/ processing clearly described on the label or in the attached form

D.5.2.1.4 Product release and reinfusion with evidence of responsible operator/s and criteria of clear and safe recipient identification

D.5.2.1.5 Methods of reinfusion

D.5.2.1.6 Traceability of the entire process

D.5.3 PRODUCT QUALIFICATION CRITERIA AND QUALITY CONTROL

D.5.3.1 Product obtained by online and offline procedures shall comply with qualifications parameters described in the specific SOP and with the national regulation. Evidence shall be shown by periodical or statistically significant planned controls that shall include at least:

D.5.3.1.1 Control frequency

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

D.5.3.2 Annually, during the Direction re-examination, a review of product management data shall be performed

D.5.4 PRODUCT DEVIATIONS MANAGEMENT

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

D.5.4.1.1 A list of know not acceptance/ deviations causes

D.5.4.1.2 Management of known causes and clinical decisions agreed about the clinical use and reinfusion of the product

D.5.4.1.3 Release and exceptional release

D.5.4.1.4 Product deviations management as an unexpected non-compliance

D.5.4.1.5 Audit on non-compliance resolution later in time (outcome analysis).

D.6 CASE HISTORY MANAGEMENT

D.6.1 TAU shall define a SOP to describe registration, management, filing of patient and performed procedures data; moreover data of adverse events and reactions occurred shall be registered and filed.
D.6.2 TAU Medical director is responsible of the clinical Case history management

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

D.6.3.1 Anamnestic data and main aims
D.6.3.2 Instrumental examinations
D.6.3.3 Diagnosis
D.6.3.4 Clinical documentation and diagnostic analysis to evaluate patient eligibility for the clinical treatment and/or possible treatment deviations
D.6.3.5 Registration of procedure data and traceability of the team that performed it
D.6.3.6 Notification of adverse event/reaction
D.6.3.7 Therapeutic plan that shall be performed
D.6.3.8 Informed consent to apheretic procedure
D.6.3.9 Registration of infusional or pharmacological treatment performed during the procedure

D.6.4 TAU shall define the place where history cases are filed, with respect to national and international laws and regulations in force.

D.7 THERAPEUTIC APHERESIS PROCEDURE

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

D.7.1.1 Operative instructions of apheretic procedure, including materials used, assembly / disassembly of circuits, priming step, startup, reinfusion;
D.7.1.2 Planning and management of apheretic technology used;
D.7.1.3 Central venous catheter management
D.7.1.4 Liquid replacement management;
D.7.1.5 Early stop of the procedure and expected procedure deviations management
D.7.1.6 Operative procedure data management
D.8 PEDIATRIC PECULIARITIES
D.8.1 Personnel of a pediatric TAU must ensure specific expertise
D.8.2 Pediatric TAU room shall be comfortable with children and parents. Special attention must be paid to maintenance of the children’s cooperation
D.8.3 Pediatric TAU shall describe a procedure for maintenance a constant intravascular volume during apheretic procedure. Extracorporeal volume should not exceed 15% of the total blood volume
D.8.4 Pediatric TAU shall describe operative instructions of management of circuit priming with leukofiltered and irradiated red cells for low weight patient or all patients with anemia, unstable blood pressure or with hypovolemia.
D.8.5 Pediatric TAU shall describe procedure that manage venous access including a policy for choosing of CVC size
D.8.6 Pediatric TAU shall describe a protocol to avoid complications of anticoagulation; Ionized calcium levels should be tested every 60'.
D.8.7 All materials shall be suitable and validated for pediatric use

D.9 EMERGENCY AND COMPLICATIONS MANAGEMENT
D.9.1 TAU shall describe procedure that manage emergency/urgency events while performing TA procedure
D.9.2 TAU personnel shall be adequately informed and formed and periodically updated on management of urgency/emergency/complications/accident that can occur
D.9.3 TAU shall define an immediate availability of drugs and medical devices to ensure the highest safety level for patient and the highest support for cardiac resuscitation
D.9.4 To ensure the highest level of safety for personnel and patients TAU shall produce at a minimum the following documents:
   D.9.4.1 Alarm management
   D.9.4.2 Type of complications and management
   D.9.4.3 Clinical intervention of intensive care personnel
D.9.5 Moreover, it is necessary to:
   D.9.5.1 Define responsibilities and extension of control/monitoring of the patient during and post apheresis
D.9.5.2 Define potential accidents related to materials, devices and equipment used during the TA procedure and the corrective action to be introduced for a rapid intervention.

D.10 DISPOSAL MANAGEMENT
D.10.1 TAU shall define a SOP about disposal of medical waste management which describes collection, transportation, disposal with respect for the environment.
D.10.2 In the case of an accidental contamination by hazardous materials, TAU shall define emergency procedures for sanitization and decontamination.

D.11 CRITICAL MEDICAL DEVICES AND EQUIPMENT MANAGEMENT
D.11.1 All materials supplied, considered as critical for patient health, shall be validated by manufacturer (according to technical specifications of the field) and manuals documentation and technical sheets related, that ensure for materials reliability and qualification, shall be attached.
D.11.2 TAU shall produce a list of all critical materials (at least apheresis kit, labels, detergents) and their process of validation.
D.11.3 TAU shall have a SOP describing supply, management, identification, qualification, control, storage process of all critical materials listed (this SOP shall indicate specific responsibilities of charge/discharge of materials and the expiry date management).
D.11.4 The SOP shall describe also:
   D.11.4.1 Minimum stock for each product
   D.11.4.2 Periodical (at least monthly) expiration plan
D.11.5 TAU shall define policy for the isolation of non-compliant or aberrant products and how to notify to competent authority the possible use of these products.
D.11.6 All critical materials shall be stored in areas, rooms, devices appropriate to prevent quality alterations.

D.12 RECORD KEEPING
D.12.1 GENERAL
D.12.1.1 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, TAU shall provide a
system to ensure immediate and unambiguous identification of 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 with an organized system and a list of content shall be produced to easily identify them

D.12.2 MANAGEMENT OF HARDCOPY ARCHIVE

D.12.2.1 Documentation shall be kept in order to ensure adequate check and interpretation during audit

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

D.12.2.2.1 Glass shield (if applicable)
D.12.2.2.2 Controlled access
D.12.2.2.3 Fire protection system

D.12.2.3 Case history shall be archived for 30 years

D.12.3 ELECTRONIC FILING OF DOCUMENTS

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

D.12.3.1.1 The latter shall be validated before being used
D.12.3.1.2 Validation shall be documented

D.12.3.2 Electronic filing 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 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 any case approved by the Director of the TAU

D.12.4 BACK UP AND SECURITY OF ELECTRONIC SYSTEM

D.12.4.1 TAU shall have a backup system to ensure the recovery and maintenance of entire documentation

D.12.4.2 TAU shall have emergency procedures in case of accidents to retrieve entire 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: OUTCOME AND INDICATORS

E.1 OUTCOME

E.1.1 TAU shall define efficiency/inefficiency evaluation criteria for treatments performed, monitoring the progress achieved annually.

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

E.2 INDICATORS

E.2.1 TAU shall ensure a continuous monitoring of its activity highlighting:

  E.2.1.1 Progress of activities
  E.2.1.2 Achievement of the objectives set out
  E.2.1.3 Perpetual quality improvement

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

F. PART F: APPLICATION OF TAU STANDARD IN JACIE-ACCREDITATED HPC-APH COLLECIION UNIT ALSO INVOLVED IN GENERAL APHERESIS

In those cases in which the TAU standard will be applied and verified in a unit where JACIE-accredited activities are performed together with other apheretic procedures that have been successfully subjected to the quality system assurance provided by JACIE 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 rules for all apheretic procedures, including HPC-Aph collection procedures.

F.2 The competency and training of all TAU staff, including the TAU Director according to the rules of the present standard performed by TAU and minimal required volume activity/year to be accredited as a TAU by present standard.

F.3 The biological product management for non HPC-Aph collection procedures, according to the present standard.

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

F.5 The full application of all mandatory indicators, including those specifically created for HPC-Aph collection procedures (Annex1).
ANNEX I: a) Table of procedure and outcome indicators
The following indicators are intended as:
**Yellow**: recommended indicators; **Green**: mandatory indicators

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Obligatoriness</th>
<th>Checked activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicators for therapeutic procedure demand and availability</td>
<td>recommended</td>
<td>mandatory</td>
</tr>
<tr>
<td>Number of bed-side procedures by TAU/ number of total procedures performed</td>
<td>recommended</td>
<td>extramural activity</td>
</tr>
<tr>
<td>Number of emergency procedures by TAU/number of total procedure performed</td>
<td>recommended</td>
<td>emergency activity</td>
</tr>
<tr>
<td>Time from procedure initial demand to the start of the first therapeutic course</td>
<td>recommended</td>
<td>Organizing efficiency</td>
</tr>
</tbody>
</table>

**Resource indicators**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Obligatoriness</th>
<th>Checked activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAU total procedures/TAU physicians</td>
<td>recommended</td>
<td>workload personnel appropriateness</td>
</tr>
<tr>
<td>TAU total procedures/TAU nurses and technicians</td>
<td>recommended</td>
<td>workload personnel appropriateness</td>
</tr>
<tr>
<td>Total TAU procedures/number of TAU separators</td>
<td>recommended</td>
<td>rate of separators utilization</td>
</tr>
</tbody>
</table>

**Activity indicators**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Obligatoriness</th>
<th>Checked activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of TAU total procedures/number of procedures required by the standard</td>
<td>mandatory</td>
<td>standard implementation</td>
</tr>
<tr>
<td>number of TAU procedures / physician / year</td>
<td>mandatory</td>
<td>standard implementation</td>
</tr>
<tr>
<td>number of TAU procedures/ nurse-technician / year</td>
<td>mandatory</td>
<td>standard implementation</td>
</tr>
</tbody>
</table>

**Outcome indicators**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Obligatoriness</th>
<th>Checked activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent annual variations of insertion of venous catheters (number of patients with an inserted catheters/total number of patients)</td>
<td>mandatory</td>
<td>Evaluation of modalities for vascular accesses</td>
</tr>
<tr>
<td>number of moderate-severe adverse reactions/number of total procedures</td>
<td>mandatory</td>
<td>clinical risk</td>
</tr>
<tr>
<td>Number of delivered satisfaction questionnaires to customers/number of questionnaires given back by customers</td>
<td>mandatory</td>
<td>customer feedback</td>
</tr>
<tr>
<td>number of complaints per year</td>
<td>recommended</td>
<td>customer satisfaction</td>
</tr>
<tr>
<td>number of patients with ASFA category I II III/total number of patients(index stratified for a single category or aggregated for all categories)</td>
<td>mandatory</td>
<td>clinical appropriateness</td>
</tr>
<tr>
<td>number of patients with efficacious/inefficacious apheresic course / total number of patients</td>
<td>mandatory</td>
<td>Clinical outcome</td>
</tr>
<tr>
<td>Number of interrupted procedures /total number of procedures (for patients' complications)</td>
<td>mandatory</td>
<td>Processes for patients' apheresic care</td>
</tr>
<tr>
<td>Number of interrupted procedures /total number of procedures (for procedure complications/malfunctioning)</td>
<td>mandatory</td>
<td>Machine and alarm management</td>
</tr>
<tr>
<td>Number of total adverse events/ number of total procedures</td>
<td>mandatory</td>
<td>Quality improvement</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Outcome indicators</th>
<th>Code</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of collection procedures to obtain an autologous graft</td>
<td>mandatory</td>
<td>Apheretic efficacy</td>
</tr>
<tr>
<td>number of collection procedures to obtain an allogeneic graft</td>
<td>mandatory</td>
<td>Apheretic efficacy</td>
</tr>
<tr>
<td>Average number of CD34+ cells/ml immediately before patients’ first PBSC collection</td>
<td>mandatory</td>
<td><strong>Timing</strong> Appropriateness</td>
</tr>
<tr>
<td>Average number of CD34+ cells/ml immediately before donors’ first PBSC collection</td>
<td>mandatory</td>
<td><strong>Timing</strong> Appropriateness</td>
</tr>
<tr>
<td>Percent of patients requiring Mozobil addition</td>
<td>mandatory</td>
<td>Appropriateness</td>
</tr>
<tr>
<td>Average patients’ blood volume processed per PBSC procedure (expressed as ml/kg) if applicable (in case of LVL)</td>
<td>recommended</td>
<td>Methodological appropriateness</td>
</tr>
<tr>
<td>Average donors’ blood volume processed per PBSC procedure (expressed as ml/kg of recipient) if applicable (in case of LVL)</td>
<td>recommended</td>
<td>Methodological appropriateness</td>
</tr>
<tr>
<td>Ratio CD34+ cell measured/predicted yield in case of prediction methods</td>
<td>recommended</td>
<td>Methodological appropriateness</td>
</tr>
<tr>
<td>Average percent collection efficiency of autologous PBSC collections</td>
<td>mandatory</td>
<td>Efficiency</td>
</tr>
<tr>
<td>Average percent collection efficiency of allogeneic PBSC collections</td>
<td>mandatory</td>
<td>Efficiency</td>
</tr>
<tr>
<td>Average number of granulocytes (PMN) in autologous PBSC collections expressed as PMN x $10^9$ for each single apheretic procedure</td>
<td>recommended</td>
<td>Procedure selectivity</td>
</tr>
<tr>
<td>Average volume of RBC (expressed in ml) contaminating each autologous PBSC collection</td>
<td>recommended</td>
<td>Procedure selectivity</td>
</tr>
<tr>
<td>Average volume of RBC (expressed in ml) contaminating each allogeneic PBSC collection in case of major ABO mis-match</td>
<td>recommended</td>
<td>Procedure selectivity</td>
</tr>
<tr>
<td>Number of microbiological positive testing post collection</td>
<td>mandatory</td>
<td>Safety</td>
</tr>
</tbody>
</table>