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QUALITY AND ACCREDITATION IN CELLULAR THERAPY

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ABSTRACT

Quality in a Health System as we know it today can trace its origins back to the early twentieth century, when a number of measures were taken to address great variations in medical education and care. The complexity of hematopoietic cell transplantation (HCT) as a medical technology and the frequent need for close interaction and interdependence between different services, teams and external providers (donor registries, typing laboratories, etc.) distinguish it from many other medical fields. The implementation of a Quality Management program with its components including quality control, quality assurance, quality assessment and quality improvement advances the quality of service provided for patients and helps programs to address external threats and internal weaknesses, which could negatively impact services and products. In HCT, different stakeholders have been identified as holding an interest in ensuring that patients receive quality care: patients and their families, referring physicians, payers, other community healthcare providers, commercial suppliers, regulatory authorities, insurance payers and professional and patient organizations. Evidence does exist for HCT, where studies using European HCT registry data have correlated the different phases of preparation for and achievement of accreditation at centre level with incremental improvements in patient survival and reduction in procedural mortality. It also proves the level of commitment to high-quality measures and monitoring cellular therapy practice and patient care. This Manual chapter will deepen the theme of quality in cell therapy, as discussed in the Consensus 2021 of SBTMO, in order to stimulate the development of quality in the centers, as well as to give a north in the proper deployments. We will briefly go through all the steps of the implementation of quality in a Stem Cell and Cell Therapy Center.

Keywords: Stem Cells. Cell Therapy. Hematopoietic Cell Transplantation.

INTRODUCTION

Quality in healthcare as we know it today can trace its origins back to the early twentieth century, when a number of measures were taken to address great variations in medical education and care. The WHO defines quality of health care as "the extent to which health care services provided to individuals and patient populations improve desired health outcomes"[1].

The complexity of haematopoietic cell transplantation (HCT) as a medical technology and the frequent need for close interaction and interdependence between different services, teams and external providers (donor registries, typing laboratories, etc.) distinguish it from many other medical fields. At around the turn of the millennium, recognition of these challenges led to efforts by the HCT community to standardize processes based on consensus to better manage quality, including the inherent risks of HCT[1].

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gram with its components including quality control, quality assurance, quality assessment and quality improvement advances the quality of service provided for patients and helps programs to address external threats and internal weaknesses, which could negatively impact services and products. In HCT, different stakeholders have been identifed as holding an interest in ensuring that patients receive quality care: patients and their families, referring physicians, payers, other community healthcare providers, commercial suppliers, regulatory authorities, insurance payers and professional and patient organizations[1,2].

Evidence does exist for HCT, where studies using European HCT registry data have correlated the different phases of preparation for and achievement of accreditation at centre level with incremental improvements in patient survival and reduction in procedural mortality. It also proves the level of commitment to high-quality measures and monitoring cellular therapy practice and patient care[1,2].

STANDARDS AND QUALITY

A standard has been defined as "a desired and achievable level of performance against which actual performance is measured". Standard-setting organisations also consider themselves as facilitators of the evolution from compliance towards improvement[1,3].

Conformance to generally accepted quality standards and external accreditation and regulation rules is fundamentally important for patient safety, efficient use of resources and best possible process outcome. Compliance with such requirements includes developing a quality plan for the organization. It sets the conditions for a review of objective evidence to demonstrate that processes and products consistently meet predetermined specifications[2].

A quality management system (QMS) is a mechanism to ensure that procedures are being carried out in line with agreed standards with full participation by all staff members. In a cell transplant programme, this ensures that the clinical, collection and laboratory units are all working together to achieve excellent communication, effective common work practices and increased guarantees for patients. It is a means of rapidly identifying errors or accidents and resolving them so that the possibility of repetition is minimised. It assists in training and clearly identifies the roles and responsibilities of all staff. The quality system should monitor processes and operations through the performance of self-assessment audits, error management, and customer feedback[1,3,4].

ACCREDITATION

AABB, FACT and JACIE set voluntary cellular therapy standards,with accreditation cycles of two, three and four years, respectively. The College of American Pathologists (CAP) transfusion medicine checklist includes cellular therapy requirements. The National Donor Marrow Program (NMDP) standards set forth basic guidelines and requirements for programs working with the NMDP. The standards encompass network participation criteria with requirements for transplant centers, recruitment centers and product collection centers. Lastly, The Circular of Information for the Use of Cellular Therapy Products is jointly written by the multiple organizations[2].

FACT (Foundation for the Accreditation of Cellular Therapy) was founded in 1996 by the American Society for Transplantation and Cellular Therapy (ASTCT) and the International Society for Cell and Gene Therapy (ISCT), published the first edition of Hematopoietic Cell Standards that year, and initiated the North American inspection and accreditation program based on these Standards in 1997. JACIE (Joint Accreditation Committee of ISCT and EBMT) was established in 1999, adopted the first edition of FACT Standards, and jointly reviewed the second edition in 2002. Subsequent editions of Standards have been jointly developed, and published by FACT and JACIE[5].

The accreditation process is divided into three phases:

The first phase is a preinspection phase where the applicant submits the relevant documentation, Application Form, Self-Assessment Standards Checklist and the inspectors review it in advance of the inspection.

The second phase is an inspection phase, where the inspectors assess on-site if the documentation from the preinspection phase meets the reality of the day-to-day work in the centre through interviews with key personnel, tour of the facilities and review of additional documentation. Inspectors document fndings and observations in the inspection report, which is reviewed by the accreditation committee which decides on the next steps for the centre to achieve the accreditation.

The third phase is a post-inspection phase, where the applicant submits evidence of corrections for the deficiencies identifed in the report. The programme achieves compliance once the inspectors assess the evidence of corrections, the standards are compliant and the accreditation committee gives the approval[1].

The JACIE and FACT accreditation systems are based on the regular update of standards covering the entire transplantation process, from the selection of the donor/ patient to the follow-up, including collection, characterization, processing and storage of the graft. And have included new items specifically developed for other cellular therapy products, with special reference to immune effector cells (IEC). Considering the different competences included in the process, the standards are articulated in 4 parts: Clinical Programme, Bone Marrow Collection, Apheresis Collection and Processing Facility. A Quality Management section is embedded in each part, aimed to provide a tool for both the applicants to develop a comprehensive quality system and the inspectors to check the compliance of the transplant programme to the standards[1].

GENERAL STANDARDS

Here, there is a summary of the main FACT/JACIE standards:

- The Program shall consist of an integrated medical team, with common staff training, protocols, Standard Operating Procedures, quality management systems, clinical outcome analyses, and regular interaction among all clinical sites[5];

- It shall use cell collection and processing facilities that meet FACT/JACIE Standards. Each facility (Clinical, Collection and Processing Lab) shall have a designated team that includes a Program Director, a Quality Manager, and a minimum of one (1) additional staff member[5].

- Apheresis and Processing Facilities shall have also a Medical Director. This team shall have been in place and performing cellular therapy for at least twelve (12) months preceding initial accreditation[5].

FACILITY

Adequate environmental conditions must be maintained at all times, with adequate equipment and materials for the procedures performed. Most supplies and equipment have required storage temperatures for optimal performance. A process should be in place to notify the appropriate departments when conditions do not meet established criteria. Facility cleaning and sanitation should also be documented. The Program shall have a written safety manual that includes instructions for action in case of exposure to different hazards, instructions for waste disposal and for use of personal protective equipment[3-5].

The Collection and Processing Facilities shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products and shall have a written assessment of critical parameters (as temperature, humidity, air quality, and surface contaminants). There shall be secured and controlled access to designated areas for the collection and processing procedures and for storage of equipment, supplies, and reagents. Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present[5].

There shall be designated outpatient and inpatient care areas that protects the patient from transmission of infectious agents and allows for appropriate patient isolation; confidential examination and evaluation; and administration of intravenous fluids, medications, or blood products[5].

Another important point, specially in case of complications, is the prompt access of patients to an intensive care unit or emergency services, renal support, use of appropriate blood products and a pharmacy providing 24-hour availability of medications needed for the care of cellular therapy patients[5].

PERSONNEL

- Facility Director and Medical Director: the Director shall be a physician or a person with equivalent degree in a relevant science, appropriately licensed and specialized, with a minimum of two (2) years of experience; and shall participate in a minimum of ten (10) hours of educational activities related to cellular therapy annually. The Facility Director shall be responsible for all elements (administrative and clinical operations) of the design of the facility, including quality management. The Facility Medical Director is a licensed physician with a minimum of two (2) years postgraduate certification, with training and practical and relevant experience for the scope of activities carried out[5].

- Attending Physicians: shall be appropriately licensed and specialized and shall have had a minimum of one (1) year of supervised training in the management of transplant and cellular therapy patients[5].

- Programs performing pediatric transplantation shall have a transplant team trained in the management and collection of pediatric patients[5].

- Nurses: The Program shall have adequate number of nurses formally trained and experienced in the

management of patients receiving cellular therapy, with specific training and maintainance of competence in the transplant and cellular therapy-related skills that they practice[5].

- Pharmacists: shall be licensed and knowlegdeable in the care of patients receiving cellular therapy, including adverse events, therapeutic drug interactions and adjustments[5].

- Consulting Specialists: from key disciplines who are capable of assisting in the management of recipients and donors requiring medical care[5].

- Quality Manager: to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with the Standards[5].

- Data Management Staff: sufficient to comply with the Standards.

Support Services: Dietary, Social Services, Psychology and Physical therapy staff with appropriate training and education to assist the patients[5].

- Training must be completed prior to an employee performing a task independently and must be repeated at defined intervals.Personnel must be assessed following training to ensure they are competent to perform the tasks for which they are responsible. Elements of competency assessment include direct observation of routine procedures, evaluation of problem-solving skills, written or oral tests[3,4].

- The following policies and processes are required by regulatory and accreditation agencies: Job descriptions and employee qualifications; Orientation; Training; Assessments of competence; Continuing education. Continued competency for each critical function performed has to be assessed annually at a minimum[3-5].

QUALITY MANAGEMENT

- There shall be an overall Quality Management Program that incorporates key performance data from clinical, collection, and processing facility quality management; and the Program shall establish and maintain a written Quality Management Plan[5].

- The Program Director shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program, at a minimum, quarterly and annually review its effectiveness. Performance data and review findings shall be reported to key positions and staff[5].

Planned deviations shall be pre-approved by the Program Director and reviewed by the Quality Manager[5].

- Data and records: The Program shall collect and maintain complete and accurate data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT[5].

- The Program shall maintain a current listing of all critical electronic record systems and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records[5].

- The Quality Management Plan shall include or reference:

  - An organizational chart of key positions

  - Personnel requirements for each key position in the Program

  - A comprehensive system for document control, with identification of the types of documents that are considered critical (SOPs, worksheets,forms, labels, etc). Critical documents should have a standardized format, an unique identifier, review every two years and a system for document approval, change control, archival, retraction and protection from unauthorized modification.

  - Maintenance of written agreements with external parties providing critical services

  - Review of outcome analysis and cellular therapy product efficacy, including time to neutrophil and platelet engraftment, incidence of GVHD, catheter infection and overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration.

  - A schedule of audits of the Program's activities to verify compliance with elements of the Quality Management Program.

  - Management of cellular therapy products with positive microbial culture results.

  - Management of occurrences (errors, accidents, deviations, adverse events, adverse reactions, and complaints)

  - Cellular therapy product chain of identity and chain of custody that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

- Actions to take in the event the Program's operations are interrupted.

- Qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services.

- Validation or verification of critical procedures: processing techniques, cryopreservation procedures, marrow or other cellular collection procedures, testing, labeling, storage, distribution, preparation for administration, and infusion at minimum.

- Evaluation of risk in changes to a process.

- Methods for obtaining feedback[5]

AUDITS

- An audit can be defined as a documented, systematic evaluation to determine whether approved policies or standard operating procedures have been properly implemented and are being followed[1].

- Audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems and shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions. They shall be performed annually at a minimum[5].

OCCURRENCES

- The management of occurrences shall include:

  - Detection

  - Investigation: shall identify the root cause and a plan for short- and long-term corrective and preventive actions.

  - Documentation

  - Reporting: to the donor's and recipient's physician(s), other facilities participating in the manufacturing of the cellular therapy product and governmental agencies as required by Applicable Law.

  - Corrective and preventive action[5].

VALIDATIONS

- Validation is a documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes[3,4].

- Each validation shall include:

  - An approved plan.
  - Acceptance criteria.
  - Data collection.
  - Evaluation of data.
  - Summary of results.
  - References.
  - Review and approval5.

STANDARD OPERATING PROCEDURES (SOPS)

- The Program shall establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management[5].

- SOPs shall be sufficiently detailed, unambiguous and describe clear objectives, equipment and supplies used, acceptable end-points, a stepwise description of the procedure, references and documented approval. SOPs that are relevant to processes being performed shall be readily available to the facility staff. Staff review, training and competency shall be documented[5].

- When genetically modified cellular therapy products are utilized in the Clinical Program, the program shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including disposal. There shall be policies and Standard Operating Procedures addressing the administration of immune effector cells and management of complications[5].

- The organization must establish a process to adress emergency preparedness. It's important to have a written disaster plan, that should be reviewed and tested on a regular basis[3,4].

DONOR AND RECIPIENT CARE

- There shall be written criteria for allogeneic and autologous donor selection, evaluation, and management by trained medical personnel[5].

- The donor and the recipient have to sign an informed consent. Informed consent is a process wherein the physician engages the donor/patient in a discussion and discloses information in a manner permitting the patient to make a knowledgeable decision about the proposed procedure/treatment. The following should be discussed: the nature and purpose of the procedure, its risks and benefits, the alternatives, the likelihood of achieving the treatment goals. The procedures shall be explained in

terms the donor can understand and he shall have the opportunity to ask questions, to refuse to donate or withdraw consent[3-5].

- Laboratory testing of all donors shall be performed by a laboratory that is accredited or licensed, using donor screening tests, HLA typing and pregnancy test in accordance with Applicable Law[5].

- Collection from a donor who does not meet collection safety criteria or an ineligible allogeneic donor shall require documentation of the rationale for his/her selection by the donor's physician and documentation of the informed consent of the donor and the recipient. If central venous access is required, the rationale shall be documented in the donor's records[5].

LABELS

- Cellular therapy products shall be identified by name according to ISBT 128 standard terminology or Eurocode[5].

- ISBT 128 provides a uniform coding and labeling system that is used worldwide. It provides traceability of all medical products of human origin including blood, bone marrow and tissues. ISBT128 provides a standard format and appearance for labeling that includes a unique Donation Identification Number (DIN) and standardized product descriptions, as well as information such as ABO and RhD blood groups, the appropriate biohazard and warning labels, collection date and time and expiration date and time[3-5].

- Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels, with a version control and checks in labeling procedures to prevent errors in the transferrence of information. Labeling elements required by Applicable Law shall be present[5].

PROCESS CONTROLS

- An organization's process control measures must include checks and balances that assist in identifying when all is well and when the process is in danger of failing or has failed. Written policies for all operational tasks must exist and should be reviewed regularly to ensure what is written is actually what's being practiced[3,4].

EQUIPMENT

- All equipment must be uniquely identified and its use documented as far as which tests, processes, or patient procedures were performed on it. This allows for traceability and troubleshooting. The following documentation should always be available: Selection (evaluation of the equipment before the purchase with a Supplier Qualification Process); Installation Qualification; Operational qualification; Performance qualification; Calibration; Preventive maintenance; Cleaning[3,4].

- When the equipment arrives, it first needs to be evaluated to ensure the device performs per the manufacturer established specifications, the process of **qualification**. Once qualified, the equipment is then inserted into it intended role in a process. The process is then **validated**. Data is collected to ensure that the process with the new equipment is functioning according to the acceptance criteria[2].

- The department's computers and software are also considered equipment. The quality plan should state who is responsible for installing, managing and maintaining the computer systems. Important processes like validation, staff access and downtime must be clarified, along with identifying the process for upgrades, backups and access removal of unauthorized personnel[3,4].

SUPPLIER AND CUSTOMER ISSUES

- Characteristics or functional requirements for critical materials have to be defined along with the ability of vendors/suppliers to meet these requirements. There should be processes in place for: Contract or agreement review; Service review; Receipt, inspection, and testing of incoming supplies. Criteria must be established for accepting critical materials[3,4].

CELLULAR THERAPY PRODUCT STORAGE

- Collection and Processing Facilities shall control and secure storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products. Conditions and duration of storage of all cellular therapy products shall be validated with a written stability program that annually evaluates the viability and potency of cryopreserved cellular therapy products. Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures[5].

TRANSPORTATION AND SHIPPING

- Shall be designed to protect the integrity of the product and the health and safety of individuals in

the immediate area, using a validated container at a temperature defined in a SOP[5].

RECEIPT AND DISTRIBUTION

- Standard Operating Procedures shall be established and maintained for acceptance, rejection, inspection, verification of appropriate transport and quarantine of cellular therapy products.[4]

- Each cellular therapy product shall meet pre-determined release criteria prior to distribution. The cellular therapy product distribution records shall permit tracking and tracing of the cellular therapy product.[4]

RECORDS

- A records management system shall be established and maintained to facilitate the review of records, and preserve their integrity, preservation, retrieval and confidentiality.The facility shall follow good documentation practices. For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record systems are not available[5].

- Retention of records is dictated by regulatory and accreditation standards although an organization can choose to be more stringent[3,4].

DISPOSAL

- Disposal of cellular therapy products shall include a pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal[5];

- Documentation of no further need for the cellular therapy product before any product is discarded and a method of disposal and decontamination that meets Applicable Law for disposal of biohazardous materials and/or medical waste are necessary[5].

Note: Some parts of the text, either highlighted by the bibliographic indication or in quotation marks, were often written as the source text of the manual FACT-JACIE. This was necessary, because there are definitions, statements and standards , that cannot be interpreted. They have to reported *Ipsis litteris* as at source.

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