Quality Management and Accreditation in Hematopoietic Stem Cell Transplantation and Cellular Therapy: The JACIE Guide

Mahmoud Aljurf
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Editors

JACIE
Joint Accreditation Committee
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Introduction

For over 20 years, transplant professionals all over the world have been working with the FACT-JACIE Standards for haematopoietic stem cellular (HSC) therapy as a means to improve the care and services provided to their patients and donors and as a framework within which to pursue continuous improvement. The FACT[1] and JACIE[2] accreditation schemes stand out for the high take-up among centres not only in high-income countries but also the increasing interest in quality among transplant professionals in low- to medium-income countries.[3] This success is testimony to the efforts of the community as a whole.

The ongoing evolution of the standards over the years demands that quality management systems can adapt to new needs and requirements, not just for accreditation but also to meet changing regulations and best practice. This handbook aims to be a professional resource on how to approach those challenges faced by many transplant programmes worldwide. The intended readers are not only centres at the beginning of their quality journey but also those centres with the experience of several accreditation cycles but with staff assuming new responsibilities for quality management.

The chapters offer different perspectives on approaches to common challenges and the reader is invited to reflect on how to best incorporate and adapt them to the realities of their own institutions. The topics include, among others, good documentation practice, internal audits, validation and qualification, outcome analysis, personnel requirements, performance measurement, tracking and traceability, adverse events and CAPAs, maintaining the quality of management programme and risk management.

The authors are all professionals working in quality in cellular therapy with a combined wealth of practical experience.

[1] www.factwebsite.org

[2] www.ebmt.org/jacie-accreditation

[3] datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

In the future, JACIE, as part of the EBMT, an international collaborative peer network of professionals working in centres and as individuals in the field of clinical bone marrow transplantation and cellular therapy, intends to issue revisions of this guide and to also assess how to exploit the contents as material for ongoing training and education as part of the EBMT's wider education strategy.

JACIE (Joint Accreditation Committee – ISCT & EBMT) is the EBMT committee established for the purposes of assessment and accreditation in the field of haematopoietic stem cell transplantation (HSCT). The Committee was founded in 1998 by the then-European Group for Blood and Marrow Transplantation (EBMT) and European members of the International Society for Cellular Therapy (ISCT). JACIE largely modelled itself on the US-based Foundation for the Accreditation of Cellular Therapy (FACT), established in 1996 by the ISCT and the American Society for Blood and Marrow Transplantation (ASBMT). JACIE continues to actively collaborate with FACT on maintaining standards for the provision of quality medical and laboratory practice in HSCT, and the two organisations jointly publish the FACT-JACIE international standards.

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Chapter 1
Quality and Standards for Haematopoietic Stem Cells Transplantation Programs

Eoin McGrath and Dunia Jawdat

Quality

The word "quality" emerged in the fourteenth century from the Latin "qualis" and the French "qualitie" [1]. 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 [2]. 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]

Quality itself is not a static concept – in its dynamic form, it becomes continuous improvement [3]. Furthermore, quality *assurance* (QA), concerned with compliance, should not be considered to be the same as quality *improvement* (QI), which is defined as the framework we use to systematically improve the ways care is delivered to patients [4]. Quality improvement has been further defined as "the combined and unceasing efforts of everyone – healthcare professionals, patients and their families, researchers, payers, planners and educators – to make the changes

[1] www.who.int/maternal_child_adolescent/topics/quality-of-care/definition/en/ consulted 11/06/2020.

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that will lead to better patient outcomes (health), better system performance (care) and better professional development" [5].

In 1966, Avedis Donabedian (1919–2000), one of the great pioneers of quality in healthcare, introduced the concepts of structure, process, and outcome as the basis to *evaluate* the quality of health care. "Structure" includes the settings, qualifications of providers and administrative systems through which care takes place; "process" as the components of care delivered and "outcome" as recovery, restoration of function and survival [6]. These concepts will probably be familiar to readers today even if they are not aware of their origins. In HSCT, structure would include the physical facilities where care is delivered, the experience and qualification of the medical and laboratory teams, the overall support structure and regulatory and reimbursement frameworks. Process would be how the patient and the healthcare system interact, e.g. referral from primary healthcare provider to tertiary care and necessary testing. Outcome includes the effect of care on diseases and their prevention, such as the mortality rate, the error rate and the quality of life [7].

The concept of quality management (QM) has been known since the 1950s and applied by different sectors for many years. However, in the field of cellular therapy, it is relatively new in comparison to quality assurance and quality control. The implementation of a QM programme with its components including quality control, quality assurance, quality assessment and quality improvement advances the quality of service provided for patients and helps programs and stem cell banks to address external threats and internal weaknesses which could negatively impact services and products.

In HSCT, different stakeholders have been identified as holding an interest in ensuring that patients receive quality care: patients, referring physicians, payers, other community healthcare providers, and professional and patient organizations [8].

Standards

A standard has been defined as "a desired and achievable level of performance against which actual performance is measured" [9]. Standard-setting organisations also consider themselves as facilitators of the above-mentioned evolution from compliance towards improvement [10].

In 1998, the European Society for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (ISCT) established the Joint Accreditation Committee – ISCT & EBMT (JACIE) – to develop international standards and offer an inspection-based accreditation process in the field of HSCT. JACIE is a committee of the EBMT, and its members are appointed by and are accountable to the EBMT Board and ISCT is represented through two members of the Committee. JACIE collaborates with the US-based Foundation for the Accreditation of Cellular Therapy (FACT), a non-profit corporation co-founded by ISCT and the American

Society of Transplantation and Cellular Therapy (ASTCT), which pioneered the standards and accreditation model starting in the mid-1990s in the USA. JACIE and FACT develop and maintain global standards for the provision of quality medical and laboratory practice in cellular therapy. The FACT-JACIE international standards stand out as an example of a profession-driven initiative to improve quality in transplantation which have subsequently been incorporated by third parties to support healthcare reimbursement (health insurers, social security) and authorization of treatment (regulatory authorities) processes.[2]

In 1974, the first bone marrow registry was founded in the UK, and since then many registries have been established around the world. Hence, for more than four decades, bone marrow registries have been crucial in facilitating the search for haematopoietic stem cells from adult donors or cord blood units for any patient around the world.

In 1988, three pioneers in the field of blood stem cell transplantation, John Goldman, E. Donnell Thomas and Jon J. van Rood, initiated the founding of the Cooperative Marrow Donor Programme, an international collaboration that was essential at that time and led to the official founding of the World Marrow Donor Association (WMDA) in 1994 in Leiden in the Netherlands to give all patients equal access to high-quality stem cells for clinical transplantation by providing international standards and guidelines relating to best practices in every aspect of the registry's operation promoting quality and donor safety. The WMDA established an accreditation programme for unrelated donor registries as an assurance to all organizations involved in HSCT.

Together with FACT accreditation of stand-alone cord blood banks, WMDA accreditation reassures transplant physicians in terms of the quality of product and services provided.

In 2007, EBMT, the Center for International Blood & Marrow Transplant Research (CIBMTR) and the Asian Pacific Blood and Marrow Transplantation Group (APBMT) together with WMDA among others founded the Worldwide Network for Blood and Marrow Transplantation (WBMT), a non-profit scientific organization aiming to promote excellence in stem cell transplantation, donation and cellular therapy.

Standards in cell therapy are offered through what are typically voluntary schemes such as AABB,[3] JACIE,[4] FACT,[5] NetCord[6] and Fundación CAT[7] among others and serve to promote patient care and excellence in clinical and laboratory practice by standardizing procedures for the collection, analysis, banking

[2] https://www.ebmt.org/regulations-guidelines consulted 22/07/2020.

[3] www.aabb.org/sa/standards/ consulted 11/06/2020.

[4] www.ebmt.org/jacie consulted 11/06/2020.

[5] www.factwebsite.org/ consulted 11/06/2020.

[6] wmda.info/professionals/quality-and-accreditation/netcord-fact-standards/ consulted 11/06/2020.

[7] www.catransfusion.es/.

and administration of cells for transplantation [11]. As an example, 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. 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 QM 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. Processing labs can apply independently; however, the target of the accreditation is the programme, intended as the process in its entirety, thus requiring a full integration of units, laboratories, services and professionals. Each section focuses on the competence of personnel, listing the topics for which the evidence of specific training is required and also including the minimum requirements of experience for positions of responsibility. Maintenance of competencies is also required for all professionals.

The standards are revised on a 3-yearly basis by a commission formed by experts appointed by FACT and JACIE, including specialists in HSCT administration, cell processing and storage, blood apheresis, transplant registries and QM. The standards are based on published evidence and, when this is not available, on expert consensus. A legal review and comparison with current regulations is carried out for each version. When the developmental phase is finalized, the standards are published for public review and comment before being approved by FACT and JACIE. The standards incorporate sound principles of quality medical and laboratory practice in cellular therapy, but they do not cover the legal requirements which fall to the relevant competent authorities.

The standards cover the use of different sources of hematopoietic stem cells and nucleated cells from any hematopoietic tissue source administered in the context of the transplant process, such as donor lymphocyte infusion (DLI). The inclusion of the term “hematopoietic” in the title is to define the scope of these standards due to an increasing number of accredited facilities that also support non-hematopoietic cellular therapies. Since the release of edition 6.1 in 2018, the standards have included new items specifically developed for other cellular therapy products, with special reference to immune effector cells (IEC). This reflects the rapidly evolving field of cellular therapy through mainly, but not exclusively, genetically modified cells such as CAR-T cells. The standards do not cover manufacturing of such cells but include the chain of responsibilities where the product is provided by a third party, usually a pharmaceutical manufacturer, and ensure the competence of the personnel in the management of adverse events related to the infusion and subsequent care.

Impact

What if any is the impact on clinical outcomes? – a crucial question given the effort and resources needed to establish and maintain the required standards in each transplant centre and subject to much investigation across healthcare at large [12]. Evidence does exist for HSCT where studies using European HSCT 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 [13, 14]. Evidence relating clinical trials participation and FACT accreditation in the United States also indicated a positive impact, although with some mixed findings [15].

Implementing a quality management system and achieving accreditation in the field of cellular therapy by a transplant centre prove the level of commitment to high-quality measures and monitoring cellular therapy practice and downstream patient care. This provides reassurance to patients and their families, healthcare professionals, commercial suppliers, regulatory authorities and insurance payers.

Standards-setting organizations must be alert to the risk of overburdening their users with requirements, falling behind the pace of change or losing the focus on what actually matters to patients: health, safety and optimal experience [12, 16]. Braithwaite *et al* propose the need for a new generation of standards that do not just assess compliance but also enable healthcare system transformation and sustainability [16].

Conclusion

The international take-up of specialized standards in a complex field such as HSCT is due to a number of factors: the early championing by some HSCT leaders emphasizing the need for quality measures to better control a complex process; international professional association support; the early observation at local level of the organisational impact and inclusion among national regulatory requirements. This widespread acceptance then provides a basis to present other aspects, such as standardised performance benchmarking of survival outcomes and minimal centre activity, as further means of quality improvement.

To help guard against overburdening users with unwieldy requirements, ultimately, we must keep in mind why quality – and by extension, standards – is important. Avedis Donabadian said in an interview not long before he died: “Ultimately the secret of quality is love. You have to love your patient, you have to love your profession, you have to love your God. If you have love, you can then work backward to monitor and improve the system” [17]. This simple but powerful statement captures the real purpose of quality.

Key Points

- Quality care is firmly established as a goal by healthcare professionals.
- Accreditation based on an internationally agreed standard system led by HSCT professionals is an effective tool to drive quality improvement in transplant programmes.
- Standards are regularly updated to reflect developments and innovation in practice.
- There is evidence that quality of care has been improved in HSCT by applying standards to clinical and laboratory practice.

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Chapter 2
Development of Organizational Quality Management System

Phuong Huynh and Renza Monteleone

FACT-JACIE accreditation is how a HSCT programme can demonstrate that it is performing to a required level of practice in accordance with agreed quality standards in haematopoietic cell therapy (HSCT). An essential component of accreditation is that a centre must demonstrate that it operates an effective quality management system (QMS). Development of a comprehensive quality management system is often the most challenging and time-consuming exercise that the transplant programme encounters when preparing for accreditation (Chap. 14).

The FACT-JACIE Standards define a quality management system as 'an organization's comprehensive system of quality assessment, assurance, control, and improvement'. A quality management system is designed to prevent, detect and correct deficiencies that may adversely affect the quality of the cellular therapy product or increase the risk of communicable disease introduction or transmission. It may also be referred to by other terms [1].

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. Once the required level of quality has been achieved, the

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remaining challenge is to maintain this standard of practice. With a working quality management system in place and adequate resources, the fundamental elements necessary to sustain the program are continued staff commitment and vigilance.[1]

The QMS in the FACT-JACIE standards establishes a framework for everyday delivery of HSCT (clinical, collection, processing) in the centre. It also includes guidelines for purchasing, human resources and document control related to the cellular therapy product and patient and donor management. In addition, the QMS includes the preparation of the quality management plan (QMP, or quality manual) (see also Chap. 13), writing of the SOPs, describing necessary processes and their interactions, and the preparation of templates for different kinds of documents and records that will be used (see Chap. 3). These are subjected to very careful scrutiny by management reviews (see Chaps. 6, 9, and 12), internal audits (see Chap. 4) and Corrective and Preventive Actions (CAPA) procedures to deal with and correct any non-conformities detected to keep the quality management system effective (see Chap. 11).

1. Development of a comprehensive QMS is often the most challenging and time-consuming exercise for the haematopoietic cell transplant (HSCT) programme as, at least in the first instance, it often requires a cultural shift in working, especially for the clinical HSCT service. Given the challenges, there needs to be a clear justification when implementing the QMS to motivate the team in terms of benefits of quality improvement for the team, their working patterns and facilities, and ultimately for patients. Professional pride and possible advantage relative to other treating centres from a successful accreditation or certification process may also be drivers for change in culture. The adoption of a QMS as part of the accreditation process also firms up collaboration between departments, services, registries and other 'third parties', e.g. national or regional blood services, unrelated donor collection centres and registries. Use of the QMS may also help to meet legal and other regulatory requirements of social and private health insurance systems and clinical trials. The QMS is central to achieving JACIE accreditation, which is now used by many external regulators as an indicator of quality for delivery of HSCT to patients.
2. The QMS should be designed to fit the real organisation of the HSCT program and its broader institution. This should reflect **not** *Work as Imagined* (WAI) but *Work as Done* (WAD) [2], i.e. not how a team would *like* to work but how they are *really* working. The HSCT programme will need to discuss and agree internally the organisational structure of the QMS and assign clear roles. This will inform the quality management plan (see Chap. 7) and summarise the relationships between each of the three services – clinical, collection and processing – e.g. how they are managed, where they are based, staffing and leadership, and whether external or third-party services provide services or components.

[1] www.ebmt.org/accreditation-definitions

3. The QMS will need to show the lines of communication and responsibility across and throughout the entire HSCT program and should summarise staffing and describe what is expected of them.
   - All centres' staff should have clearly defined roles and responsibilities and these should be shown on the organisational chart (Table 2.1). This could then be further explained in the QMP, especially the responsibilities, the Job Descriptions or the contact information. If staff are not directly employed by the same institution, honorary contracts may be necessary. An honorary con-

Table 2.1 List of the personnel who work within the transplant programme at the centre who could appear in the organigramme

Position
Note: not all positions listed here will be relevant to all programmes – centres should only reflect their real organisation, roles and structure
HSCT Clinical Programme Director
Clinical Adult Facility Medical Director, as applicable
Clinical Paediatric Facility Medical Director, as applicable
Adult Attending Physicians
Paediatric Attending Physicians
Junior Doctor
Physician in training
Bone Marrow Transplant Unit (BMTU) and Oncology Day Beds Unit (ODB) Senior Nurses and Education Sisters
Nursing Quality Management Lead
BMT Ward Manager
ODB Ward Manager
Clinical Risk lead
BMT Education Sister
Paediatric Haematology/Oncology Education Sister
BMTU Coordinators
Nurse Coordinator
BMT Medical Coordinator
Donor Coordinator Programme
BMT Pharmacist
Clinical Programme Quality Manager
Clinical Programme Data Manager
Clinical Programme Infection Control Lead
Apheresis Facility Medical Director
National Blood Service Quality Management
Quality Assurance Manager
Assistant Quality Assurance Manager
Processing Facility Medical Director
Laboratory Technician

tract gives individuals the right to work in more than their own institution and is good evidence of integration across different organisations.

– The FACT-JACIE standards require that the QMS includes an organigramme or organisational chart (see Chap. 7), i.e. visual representation of the structure of all parts of the HSCT programme, and makes clear who is responsible for what aspects of which services (collection/clinical/processing). It should illustrate who reports to whom and who has responsibility for the different aspects of the transplant programme (Figs. 2.1, 2.2 and 2.3). The structure will enable both new/existing staff and external organisations to easily identify the make-up of the programme and lines of authority. Patients could also be provided with information about the team who are looking after them. The HSCT programme will need to show where the collection and processing take place and the individuals involved. Third-party collection and processing services are likely to have their own QMS which is perfectly acceptable if there are service-level agreements (SLAs, Chap. 8) or contracts in place that define how the respective QMS interact.

Below is a list of roles that should be considered for inclusion in the programme organigramme and sample organisational charts showing differently structured programmes.

The Quality Assurance and Performance Improvement System is a coordinated, comprehensive and systematic plan for monitoring and continuously working to improve the services to support the care that patients receive. It will assist staff in

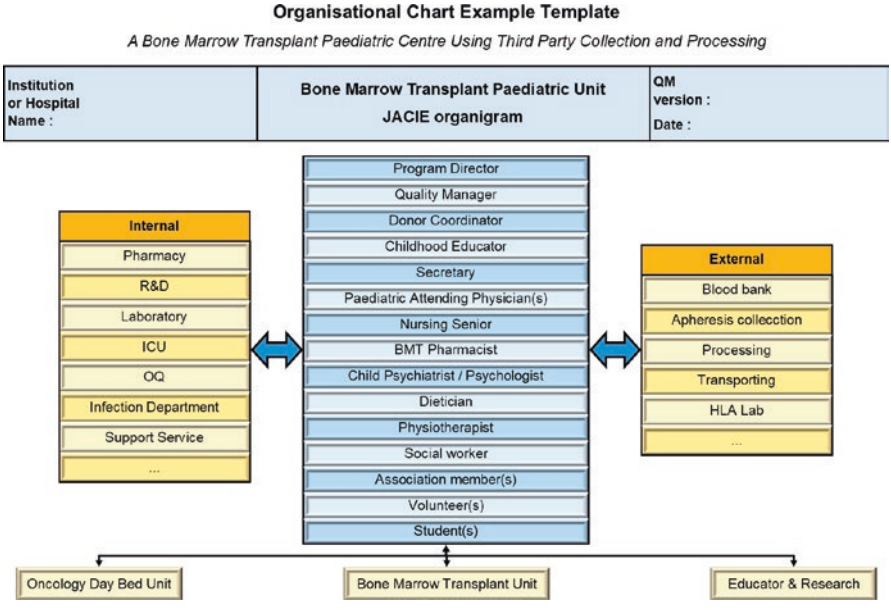

Fig. 2.1 Example 1 of organisation chart template

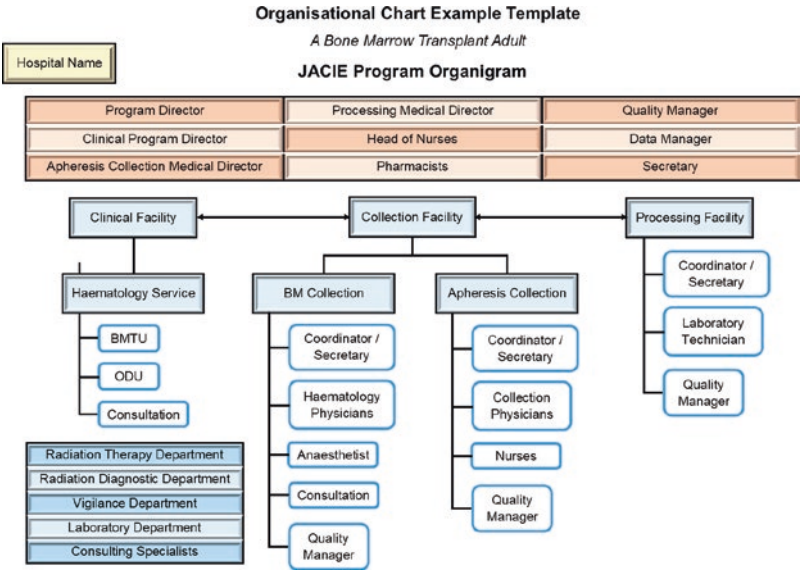

Fig. 2.2 Example 2 of organisation chart template

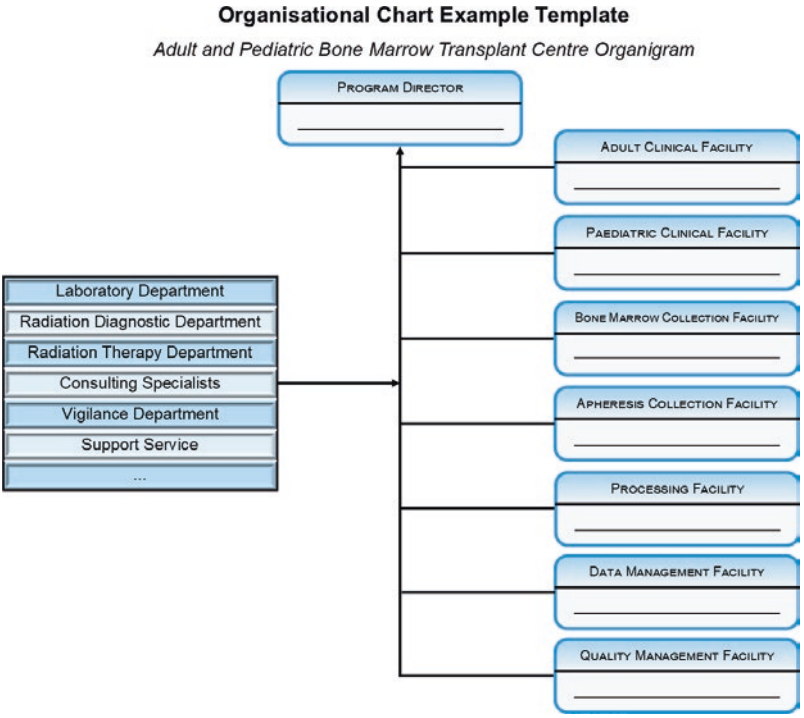

Fig. 2.3 Example 3 of organisation chart template

meeting their individualized objectives and shall be managed by the quality manager. Quality managers are responsible for the development, implementation and maintenance of the QMS, while the clinical program directors, in collaboration with the respective collection and processing directors, shall retain overall responsibility for quality.

Depending on how the HSCT programme is organised and its size, there may be a single quality manager or separate quality managers for each service, i.e. clinical, collection and processing.

Although the overall responsibility for the quality of the HSCT programme lies with the services directors, the quality manager has key roles including, but not limited to, the following:

– Understand the entire HSCT process from start to finish.
– Facilitate the development of documentation.
– Facilitate improvements to standardise and enhance the overall service.
– Support the HSCT programme director and facilities directors and educate the team in establishing and sustaining a quality management culture.
– Coordinate the quality programme.
– Report and communicate minutes of quality meetings between the clinical, collection and processing facilities, and the quality management activities at a minimum quarterly. A description of the process for annual performance review and provisions for continuing education (Chap. 17) also need to be included.
– Communicate regularly with HSCT programme staff (e.g. collection, nursing, administrative, laboratory, consultants, junior doctors, data managers).
– Be visible within the centre and motivate people with respect to quality improvement.

The quality manager must understand how the HSCT process works in various settings (allogeneic, autologous, etc.) and the steps patients and donors follow, for example:

- To understand the collection and processing part of the HSCT process, following a patient, donor and/or product through the process of stem cell collection and processing to understand the pathways for the patient/donor and the cellular therapy product.
- To understand the HSCT process from the patient's perspective, asking the patients for their opinion. For instance, did they get all the information they needed? Was the procedure as they expected?
- To understand the HSCT process from the staff perspective, observing them while they see a few patients all undergoing the same procedure, then ask questions about how and why things are done in a particular way and if there is alternative way to do it.

The quality manager must also use standardised control documents, meetings with staff from each of the services, audits as well as methods for reporting, investigating and correcting adverse events whether the HSCT service is fully integrated or comprised of three separate facilities.

One of the key aims of the QMS should be to improve communication and understanding of roles and responsibilities across all the different staff groups within the HSCT program. Poor communication between groups of staff is cited as one of the biggest single causes of quality programme failure [3]. Joint Commission sentinel events analysis between 2004 and 2014 consistently showed poor communication as a contributor to failures or inefficiencies of processes [4].

A quality programme will only be successful if there is communication between all the staff involved. Regular group and team meetings should be set up to maintain and increase integration and ensure that different systems work together (Table 2.2). The QMS and QMP are central to improving communication between staff and departments and to ensure that everybody is clear about roles, responsibilities and processes for decision-making. Examples of template agendas and signing in sheets

Table 2.2 Suggested quality groups/teams

Group	Who	What
Quality management group	Quality manager, HSCT programme director(s), medical staff, senior nursing staff, pharmacists, data managers, collection facility staff, processing facility staff, laboratory staff and clinical trials staff	SOP development/review, audit timetable development, incident reporting, training/educational programme development and service improvement
Clinical policy group *This group does not have to be separate from the Quality Management Group and could form part of the same meeting*	Quality manager, transplant physicians, nursing, pharmacy and support staff	Clinical policies
Multidisciplinary group	Transplant physicians, nursing staff, collection/processing and other support service staff	Morbidity and mortality meetings : presentations of specific cases allow treatment pathways and outcomes to be discussed
Stem cell facility user group meetings –: *in centres where a separate or third party collection and processing facility is used*	Hosted by the third-party facility to discuss issues around the service provided	The agenda can include document development where documents are linked, i.e. delivery to the centre, incidents with product delivery, biological product deviations
Other management review meetings.	All directors, quality manager, nursing and medical staff National or regional blood services, unrelated donor collection centres and registries	Look at the entire QMS in relation to other institutional organisations and HSCT referral base
Ward meetings, staff meetings, handovers, etc.	Quality manager, ward team, staff, etc.	To bring quality issues to the ward

serve as evidence of meetings, joint decision-making and integration within the HSCT programme.

Below are suggestions of the types of groups that should be contributing to the maintenance of the QMS [5].

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Chapter 3
Document Development, Implementation, Review, Archive, and Disposal

Nick van Sinderen

General

Documents have many uses in the quality management program. They provide the structure needed for quality assurance through policies and procedures, ensure quality control through forms such as pre-printed orders and worksheets, and support quality management activities through audit reports, outcome analyses, and training records. The quality program needs to identify documents critical to the transplant program. The transplant program needs to describe how the critical documents are conceived, generated, implemented, distributed, reviewed, and stored. All parts of the transplant program require written instructions as to how to undertake key processes. Equally, personnel in the facility should use these documents to carry out tasks and they need to be sure that the document they are using is the current version. Documents (policies, Standard Operating Procedures (SOPs), worksheets, and forms) are the foundation of the quality program as they explain how tasks are undertaken and facilitate the effective operation of the transplant service. An overarching policy encompassing the writing, reviewing, implementation, and control of documentation (the "SOP about SOPs") is a key requirement.

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Start

Setting up a document management system (DMS) starts with making an inventory of what you have and of what you need. What do you think is required and what are the JACIE requirements? The standards provide a structure whether you are starting from square one or whether you already have a set of transplant-related policies. Transplant centers frequently have pre-existing laboratory and, less commonly, clinical policies, though, very often, the system is so fragmented that many staff are unaware of their existence. From the outset, it is imperative to form a project team as the task is huge and needs constant monitoring and steering.

Some key points to consider:

- Use your in-house expertise
  If you make your expertise the starting point, you will make the DMS your own. In the development of documents, review the draft contents against the JACIE requirements. This will lead to useful discussions which will increase the value of your SOPs.
- Use information available in your own hospital
- Other departments in your hospital will already have information and policies that you can use as a starting point. Refer to them in your own documents and this will prevent unnecessary duplication and make yours easier to read, e.g., hygiene and safety policies.
- Don't go reinventing the wheel in developing new policies about which you know little. Ask other hospitals or EBMT quality forum colleagues whether they have information or policies that they might be willing to share. Then, modify them to suit your own requirements.
- Refer to other documents rather than continually lengthening your own new policies and procedures. This will prevent you from falling into the trap of having to constantly revise huge, unreadably large documents. Refer to checklists, papers, and key supportive information.
- Make sure that in-document URL hypertext links always relate to the source document and that they work. You can use the same link throughout your DMS.
- Use job titles rather than the names of individuals in your DMS to avoid the need for document revisions when people change jobs.

Use the quality manual as your starting point. This is a high-level document, so avoid excessive detail and try to keep it short. Refer to SOPs and other relevant documents. In your SOPs, refer to checklists and additional information elsewhere *(see Fig. 3.1)*. This makes them more readable and accessible.

Example set-up of the quality manual

1. Organizational profile (facility description)
2. Definition of the QM program
3. Impact of the quality management program
4. Aims of quality assurance
5. Organizational structure and responsibilities

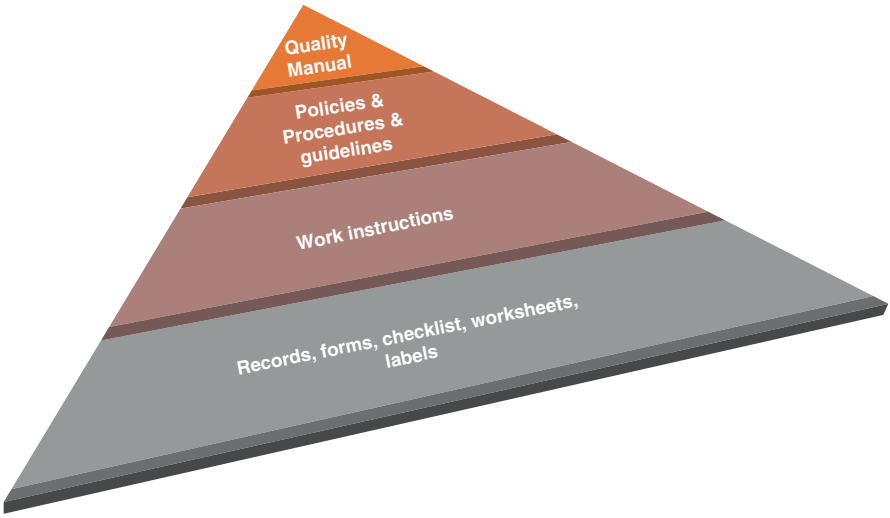

Fig. 3.1 Example document structure

6. Agreements & key relationships
7. Key personnel – roles & responsibilities
8. Personnel qualifications, training, and competency
9. Communication
10. Documentation
11. Adverse events
12. Audits
13. Outcome

Workflow

The quality manager has overview of all documents and is usually assisted by document managers who are clinicians or scientists with a part-time role in quality (see Fig. 3.2). This is a constructive approach in that such individuals have areas of expertise which relate to the documents assigned to them. They are therefore best positioned to ensure that the relevant policies are fit-for-purpose.

The quality manager is the direct link to transplant program management and is responsible for the implementation of the QMS. The quality manager provides a quarterly report to the clinical program director and the management team to keep them up-to-date regarding new documents and revised versions of existing documents. These quarterly reports are included in the annual report and the annual management review, completing the policy Plan-Do-Check-Act (PDCA) cycle for this topic.

Fig. 3.2 Create and review documents

– Author

The first author of a document leads in its preparation and writing and should have relevant expertise. The goal is to produce an advanced draft ready for wider review. This provides an educational opportunity which will be addressed further later in this chapter.

– Reviewer(s)

These are one or more individuals who check the document for factual accuracy and clinical relevance. If required, suggested improvements can be incorporated into a revised version. This person is often from another department and provides different expertise. Such a fresh perspective is often very useful. An example would be a pharmacist reviewing medical policies from the point of view of pharmacovigilance. This is a common approach and helpfully ensures that pharmacists are aware of all new treatments.

– Authorization

The clinical program director (CPD) is ultimately responsible for the transplant program and the CPD (or his/her designee) therefore authorizes all documents. However, the CPD does not necessarily need to review and authorize each document. That would take an additional work week. The non-medical documents can be delegated to members of the management team or the relevant senior, qualified individuals. In such cases, this should be carefully documented in the DMS SOP. If necessary, the CPD can review document metadata in order to monitor its development. These changes can be summarized in the quarterly and annual reports.

Note: Electronic document management systems generally allow for each step in the process to be tracked. This is not the case with paper-based or hybrid systems and care is needed in such cases to ensure that the workflow is robust and easy to operate.

Responsibilities

Involve as many staff as possible when developing new documents. This is crucial. It is common at inspections to find that the DMS has deteriorated – missed review

dates, obsolete policies – as too few people have too many documents to take care of. Tasks end up being repeatedly deferred. This can be dangerous for both patients and clinical staff as treatment protocols must be kept current and have the latest information. It is the job of the quality manager to ensure that newly authorized documents are immediately made available for routine use.

Here are some examples of the appropriate staff to be involved in developing particular policies:

- Treatment and medical and supportive care: (senior) nurse, physician-in-training, nurse practitioner, physician assistant, oncologist, hematologist, pharmacist, counselor
- Policy: management team, team leaders
- Data: secretary, data manager, nurse

Medical systems differ and you will need to adopt an approach that best suits your local circumstances. However, the key take-home message is to involve as many people as possible in order to keep the system going in the long term.

Duplication of Requirements Between Different Quality Systems

Anyone involved in quality is aware of the overlapping requirements between quality systems such as JCI, JACIE, and ISO. The transplant unit may be a component of a wider oncology program; a pharmacy-based QMS might be subject to a different regulator; the pediatric unit may be administratively distinct from the adult unit; and there are often a number of different information and communication (ICT) services networks – whether national, regional, or hospital-based – all available on local workstations. Equally, the hematology laboratory may be accredited to ISO 15189:2012 (medical laboratories – requirements for quality and competence). In general, there are few significant differences between these standards. A useful approach is to follow the stricter guideline and to try to avoid following separate regulations in a given area as it may lead to confusion. For example, if JCI requires three-yearly review and JACIE two-yearly, follow the JACIE requirement.

Unfortunately, the different international standards have evolved and diverged over time, and it is important to bear in mind when creating DMS policies that they meet all of the different regulatory requirements. Inspectors and the EBMT can be made aware of these issues.

Each transplant unit has unique circumstances, based on local logistics and resources. So it is not possible to be prescriptive. Rather, the key principles to remember are that documents need to be kept up-to-date and accessible for everyone involved. Important underlying concepts include the use of technical solutions, cross-referencing between documents to prevent redundancy, and close collaboration with other hospital departments, especially ICT, when setting up and also on an ongoing basis to maintain the DMS.

ICT Systems and Paper Documents

Recent ICT advances have included hospital-wide electronic patient records (EHRs) and remotely accessible document management systems. Some of these allow for treatment protocols to be automatically included in patient records, guaranteeing the use of the current version. More usually, however, each transplant unit is a patchwork of promising innovations and local logistical limitations. The challenge might be physical due to lack of space or financial due to inadequate investment. Some departments manage to set up their own bespoke IT systems. Although an attractive short-term solution, this can pose problems. The hospital ICT department will not provide support when something goes wrong and such a system can leave the unit dangerously reliant on one motivated individual.

A paper-based DMS offers a reasonable alternative but has some challenges of which you need to be aware. These include the revising of policies, filing and archiving, and how to keep everyone informed of new versions of documents. This is the system where you see frequent handwritten notes. If following Good Documentation Practice guidelines, every written update to a document must be signed and dated. This is not likely to happen in a hectic hematology department.

Here again, there is no one-size-fits-all solution. However, using a collaborative common sense approach, it should be possible to put in place a workable system that meets the standards. The basic question you always have to ask yourself is, "How do I get the latest version of the document to the people that use it?"

Education and Document Management

A document management system is a perfect tool for education. Here are some examples:

- New employee: make sure that new employees receive training in the DMS. Consider assigning them documents in their field of expertise. Over time, they can be assigned first authorship.
- As mentioned previously, involve pharmacists in the development of treatment protocols.
- Discuss policy changes at quality meetings. Other means of disseminating information include newsletters, reading lists, etc. If the change is significant, it could be brought to the multi-disciplinary team meeting to ensure that all staff members are informed.
- Secretaries and data analysts use data in patient files on a daily basis. Involve them in reviewing documents in their field of expertise.
- Bring different staff together for collaborative discussions. Taking people out of their silos can lead to productive cross-fertilization of ideas: "I never knew you could do it that way!"

These are just a few examples of how you can use document management systems for educational purposes. Reflect on how this can be done to benefit your program.

JACIE on Document Management

The document control policy shall address the points listed in Fig. 3.3

The JACIE document management standards are straightforward. Documents should have a standard format and should be revised every two years with clear revision dates and tracked changes. They must be authorized by the CPD or designee, contain accurate references, and information on "who modified what, at what time, and why" should be clearly recorded. Methods to ensure safe validation of both electronic and printed versions are also required. Finally, and importantly, maintain a readily available list of all critical documents.

Documents may require revision for several reasons:

- If a staff member makes a clear case for revision
- As a corrective action following an (internal) audit or adverse event
- Changes in regulations (law)
- Changes in standards
- Changes in organization

The DMS SOP should clearly describe these processes. Documents should be easily accessible. Finally, maintain open communication with all staff in the

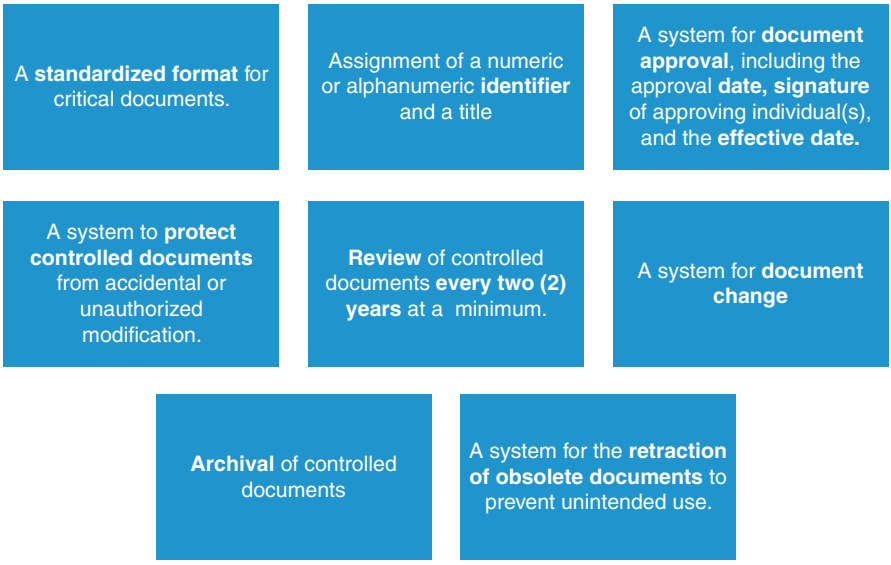

Fig. 3.3 JACIE and document management

transplant program and make sure management is aware of all significant developments.

Note: Refer to the JACIE/ EBMT manual for the standards and guidance in their implementation.

Source for figures

1. Figures 1 and 2 were created by the author, and Figure 3 is from the EBMT Standards quality management presentation.

Chapter 4
Audits

Olga López-Villar and Julie Dolva

General Concepts

Definition and Purpose

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, 2].

Audits represent one of the principal activities of the quality management program. They are conducted to establish whether the program is operating effectively and to identify trends and recurring problems in all aspects of facility operations. Of course, an audit can also demonstrate strengths.

A common mistake is to see the audit, particularly external audits, as the goal of the quality system. The idea – "I have just passed the JACIE audit so I can relax until the next one" – is a misunderstanding of what audits are for.

Scope

The scope of the audit can range from simple to complete. It can examine a particular process, the quality system itself (quality audits), or the whole program.

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The scope must be described in detail in the audit plan. Audits and the audit plan are part of the quality management system. Depending on the organization of internal audits in a center, the unit can be audited within a single (and comprehensive) internal audit or there can be different audits for different topics.

Types of Audits

Internal, third party, and external audits [3]:

- *Internal audits* are performed by an individual who works in the unit but who is not solely responsible for the audited activities (see the job requirements of an internal auditor later in this chapter).
- *Third-party audits* of vendors or suppliers may be performed to check that the provider has performed the service or provided the product according to the agreed criteria. In the accreditation manual [2], it is stated that a remote audit by questionnaire (document audit) is an example of how to qualify a vendor.

  Another example is that of units being audited by manufacturers of CAR-T cells. In this case, the unit (clinical, collection, or processing) does not perform the audit; it is analyzed by the company's auditor.

- *External audits* are performed by some entity outside the program. There are two types:
  - Performed by external certification or accreditation body: JACIE, ISO9001, etc.
  - Inspections by the competent authority

These certification or accreditation entities require internal audits to assess the system.

It would be unnecessarily time-consuming if units had to arrange dedicated internal audits to meet the specific requirements of each accreditation body. It is therefore advisable to make sure to include all requirements in the audit procedure.

Deviations detected in third-party and external audits should be managed according to the center's corrective action and preventive action (CAPA) policies in the same manner as those detected in internal audits.

Other ways of classifying audits are as follows:

- On-site vs document:

On-site The auditor visits the unit to perform the audit (on-site). The auditor may examine documents relating to the scope of the audit or procedures performed on the day of the audit, interview personnel, etc.

Document Alternatively, the audit can consist of a review of documents submitted by the center. This type of audit is not generally recommended for internal audits and is best reserved for interim audits or for audits of remote third-party providers.

- Audit for accreditation or re-accreditation vs interim audit: more details in Chap. 14 (the accreditation process).

The audits for accreditation or re-accreditation are the ones performed to check the system and obtain the accreditation.

The interim audit is performed during the accreditation cycle to assess that the quality management system is still functioning according to the standards.

This chapter is dedicated to internal audits.

Auditor Requirements

An auditor requires sufficient expertise in the subject manner to be able to identify problems and must also be a competent auditor.

Knowledge of the subject being audited is often needed to perform internal audits. The organization must be able to demonstrate how they assess auditor competency. Examples could include courses, audits performed, etc.

The auditor can be a transplant program or unit staff member as long as they are not solely responsible for the process being audited and did not perform the audited activities [2].

How to Perform Internal Audit: The Steps of an Internal Audit

The program must have a description of precisely how they perform audits, specifying for the particular unit or program all the steps that are summarized in this chapter.

Audit Calendar

There must be a calendar or schedule of audits (Table 4.1). The auditor can be included in this calendar or in another of the documents. The head of the QM program should identify areas to be audited and audit frequency [2]. The calendar should be shared with key personnel at quality meetings. Depending on the structure of the transplant program, there may be one overarching program audit schedule or each unit may develop their own calendar.

Examples of audits can include the following:

- Adherence to procedures or policies
- Completion of records
- Completion of training
- Equipment maintenance according to schedule

There are mandatory audits required by JACIE or the institution, while other audits may be based on local requirements or problems and may be identified by risk assessment, for example. There must be regular auditing of critical activities; the frequency will depend on the importance of these activities, and, to some extent, on the results [2]. There is a list of the minimum requirements in the JACIE standards. Most of the topics require an annual audit. To make it simple, annual audit for all topics is a reasonable approach.

The list of audits might have to be modified or extended during the year, for example, to include follow-up audits.

Audit Plan

Preparation and planning are important parts of a good audit and must be done thoroughly. An audit plan is prepared as a specific guideline for the audit and is essential to allow the auditor to perform an effective and efficient audit.

Depending on center procedures, auditors can use either a pre-existing checklist or a specific checklist prepared by them which includes all the items to be audited. The JACIE checklist, or parts of it, could serve this purpose, depending on the scope, and other topics can then be included depending on the unit and on the quality system in use in the unit.

The use of checklists to perform the audit is not mandatory; other tools are acceptable if they cover all the topics that are to be audited.

The plan should include the actual date, location, etc.

Conducting the Audit

Depending on the audit procedure, a formal introduction may not be necessary.

During the audit, the auditor will review the process, the procedures, forms, etc., according to the audit plan. The auditor will interview the personnel to assess if what they do is performed according to the written procedures of the unit and according to the standards [4]. During the audit, the auditor collects evidence to assess adherence to standards. For the report, it is important to write down any evidence of a deviation in a particular requirement.

Closing

Depending on the procedure, a formal closing meeting may not be required. However, it may be useful to discuss the audit findings with the individual responsible for the procedure or their designee and with the quality manager.

Table 4.1 Example of an audit calendar for the Clinical and Marrow Collection Facility

Internal audit calendar of the unit				Year:		Approved by:						Date:	
Facility	Scope	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Clinical	Accuracy of clinical data												
Clinical	Donor screening and testing												
Clinical	Cellular therapy products with positive microbial culture results												
Clinical	Etc.												
Marrow collection	Interim assessment of donor suitability and eligibility												
Marrow collection	Documentation of donor eligibility												
Clinical and marrow	Quality												

Audit Report

The audit report is an important document and must be prepared by the auditor within a pre-defined timeframe.

The use of a template (example in Table 4.2) is recommended to ensure that all the necessary details are included. These should include the following: audit title, scope, auditor, date, location, plan, copy of the checklist or of the audit findings, summary of deviations, and signatures.

Audit report form
Audit title: _____
Facility: _____
Scope: _____
Audit type (yearly, key elements, focused, follow-up, etc.): _____
Audit purpose (main aim of the audit): _____
Auditor: _____
Date: _____
Location: _____
Plan of audit: include times, questionnaires, interviews, other staff, or areas involved, etc.

Table 4.2 Example template for an audit report form. Adapted from "A practical guide to implement quality management in a Stem Cell Transplantation Programme" [5]

Auditor findings/copy of completed checklist:
Summary of deviations:
Date of the report: _____ Signature of the auditor: _____
Reviews: Quality Manager: Date, name, and signature _____ Manager of the audited area: Date, name, and signature _____ _____ Facility Director: Date, name, and signature _____

Table 4.2 (continued)

The audit report should be reviewed and approved by the appropriate personnel, such as the quality manager and the facility director. The approved audit report should be distributed to the manager of the audited area and should be shared with staff, when appropriate [2].

Internal audit reports are always reviewed in external audits (JACIE, ISO, etc.), so it is important to make sure that the necessary reports are available for the inspector.

Actions

Audits are performed to recognize problems, trends, and improvement opportunities [1], and any findings should be followed by the necessary actions. The center must identify the underlying root cause of the deviation and implement corrective and preventive actions (CAPA) (see Chap. 11) or process improvements, as required [2], ideally as soon as possible, and certainly within the required timeframe.

The corrective and preventive actions should include a scheduled date for a follow-up audit to verify that effective corrective actions have been implemented [2].

The required actions must be documented according to local procedures. The findings of the audit can be included within the established system for recording deviations, occurrences, etc. (see Chap. 11).

The center can also choose to document the actions in the audit report (Table 4.3). The effectiveness of the actions must be reviewed and documented and further audits might be necessary.

In subsequent audits, it is important to review stages in the process where deviations have previously been found to occur.

Communication of the Result of Internal Audits

The results of the audits, as a key component of the quality management system, must be shared at quality meetings and included in the annual report.

Audit results, corrective actions, and follow-up actions should be reported at least once a year. Review by the Program Director should be documented and there should be evidence that audit reports have been shared with the appropriate staff [2].

Corrective Action Plan after Audits

Audit title: _____

Facility: _____

Scope: _____

Audit type (yearly, key elements, focused, follow-up, etc.): _____

Audit purpose (main aim of the audit): _____

Date: _____

Deviation 1: _____

Underlying cause: _____

Actions: Corrective ☐ Preventive ☐

1st action: Description: _____

Responsible: _____

Due date: _____

Follow-up: _____

2nd action: Description: _____

Responsible: _____

Due date: _____

Follow-up: _____

Table 4.3 Example template for corrective action plans. This table can be added to the audit report (Table 4.2) if the center decides to include the actions in the audit report instead of including them in the deviation procedure
Adapted from "A practical guide to implement quality management in a Stem Cell Transplantation Programme" [5]

Deviation 2, etc.: _____ Same structure as in deviation 1
Reviews: Quality Manager: Date, name, and signature _____ Manager of the audited area: Date, name, and signature _____ _____ Facility Director: Date, name, and signature _____

Table 4.3 (continued)

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Chapter 5
Qualification and Validation

Renza Monteleone and Dieter Klarmann

Qualified equipment and *validated processes* ensure satisfactory, safe, and reproducible outcomes and allow personnel to achieve, within the limits of the precision of the process, the same output when starting with the same input. Any change of equipment, utilities, or process should be formally documented and the impact on the validation status or control strategy assessed (change control [Fig. 5.1]).

A process is validated by establishing objective evidence that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Process validations can be performed prospectively or concurrently.

The transplant program or facility should have a specific SOP or document (validation master plan – VMP) related to qualification and validation, detailing which validation studies are mandatory, how to perform them, and in what format. The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended.

In this SOP/VMP, the following items should be addressed:

- Scope of validation and critical processes to be validated
- Activities included in the validation plan, methods, and tools to be used to verify the reproducibility of results
- Activities to perform in the qualification of materials/supplies, facilities, equipment, and verification of personnel training

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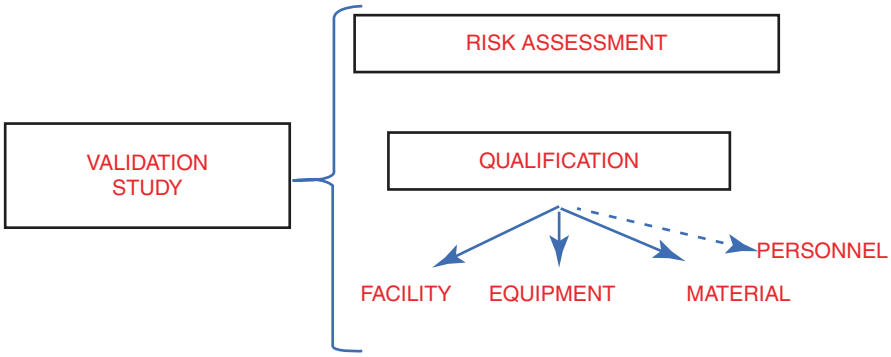

Fig. 5.1 Validation study including risk assessment and qualification

- Collection and analysis of data, tests to be performed, number of samples to be tested, range of acceptable results
- Collection and documentation of results
- Conclusions and approval of validation study
- Duration of validation and criteria for revalidation
- Change control management

The responsibility for the validation SOP/VMP lies with the director of the transplant program. However, responsibility is shared with the quality manager, who has the key role of deciding on the methodological tools to be used for qualification and validation by the professionals involved in this process. The quality manager is responsible for organizing and monitoring training and ensuring the competencies of the personnel involved in the validation studies as well as organizing training on change control and risk management. Finally, the quality manager verifies the implementation of and compliance with the validation SOP/VMP.

The result of each validation study must be reviewed and approved by both the quality manager and the transplant program director or facility director (collection, processing, or clinical) and/or by the individuals deemed responsible according to national pharmaceutical law.

All transplant program personnel should be involved in the validation studies. This can be achieved by establishing a dedicated validation team with representatives from across the transplant program. Professionals involved in the qualification and validation steps should have specific training in the relevant area and in the processes to be validated. They should collaborate with the quality manager and, if required, external experts; for example, when qualifying equipment, this may necessitate the involvement of the hospital maintenance office and the manufacturer.

A risk assessment should be performed for each validation study to assess how critical the process is and to define the level of risk.

Qualification of the facility, equipment and material, and verification of personnel training are included in the validation study (Fig. 5.1).

Validation Process (Fig. 5.2)

Identification of critical processes to be validated JACIE defines some minimal mandatory validations, though every transplant program should decide whether additional processes are critical to their activities and might therefore merit formal

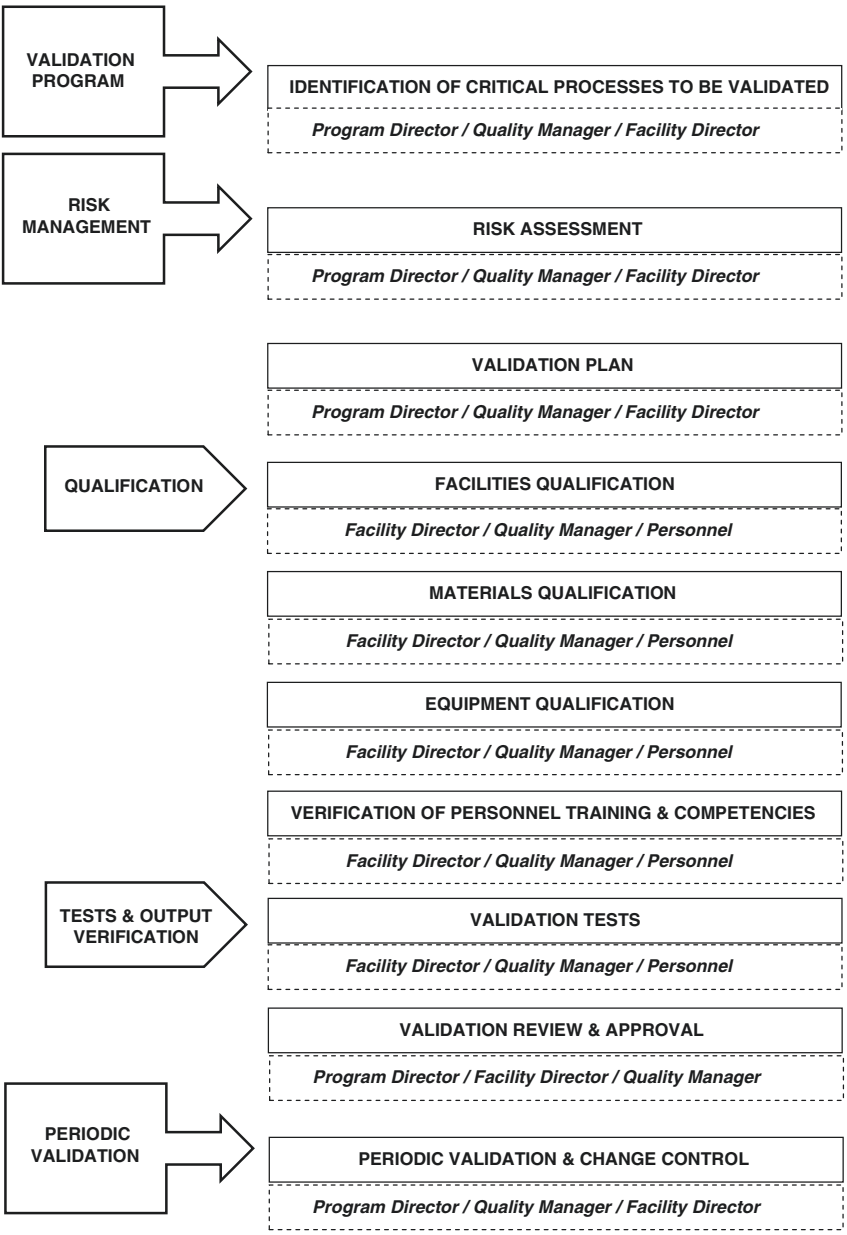

Fig. 5.2 Steps to carry out a validation study and responsibilities

validation. A process is considered critical if it impacts on the quality and/or safety of cellular products.

The minimal Validation studies required by the JACIE Standards are as follows:

- Apheresis collection
- Bone marrow collection
- Processing and cryopreservation
- Labeling
- Storage
- Distribution (included transportation and packaging)

Risk assessment Evaluation of the level of risk and activities that might mitigate this risk (see Chap. 18 on Risk Management).

Validation plan For each critical process requiring validation, the facility should produce a validation plan that includes the following:

– Rational for validation: refer to standards, applicable laws, critical nature of process, etc.
– Results of risk analysis: the facility should define the type of validation exercise based on the perceived level of risk
– The expected endpoint or result
– The different phases of validation, assignment of roles, the output for each phase and methodologies to be adopted
– List of variables to be qualified: facilities, materials, equipment, and personnel
– Method for qualification of facilities, materials, equipment, and personnel
– Operating standards (process parameters, SOP, etc.): to guarantee satisfactory ongoing supply of the process and to maintain the validation status over time
– Evidence of validation
– Validation protocol: method for collection of data and analysis, timeline, expected output, presentation of results, deviations management
– Validation documentation: registration forms, database, etc., to guarantee documented evidence of the results of the validation process
– Validation cycle planned for revalidation and requalification of equipment

Qualification: facilities, material, equipment, personnel Each component that could influence the results of the process should be qualified. Qualification of facilities, for example, is based on the verification of suitability of the rooms for the proposed activities, verification of environmental conditions, access for authorized staff, certification, etc. Qualification of materials is based on the verification of the manufacturer's certification, integrity of packaging, expiration date, etc.

Qualification stages for equipment, facilities, utilities, and systems according to [1] are listed in Fig. 5.3:

1. User requirements specification (URS)
2. Design qualification (DQ)

3. Installation qualification (IQ)
4. Operational qualification (OQ)
5. Performance qualification (PQ)
6. Requalification

Competencies The competency of personnel to perform the activities related to the process undergoing validation should be verified and, if insufficient, specific training should be arranged. The validation team should check that there are SOPs for all the processes involved in the validation study and, if unavailable, need to generate such policies; registration forms need to be available to ensure that every step of the process can be clearly traced.

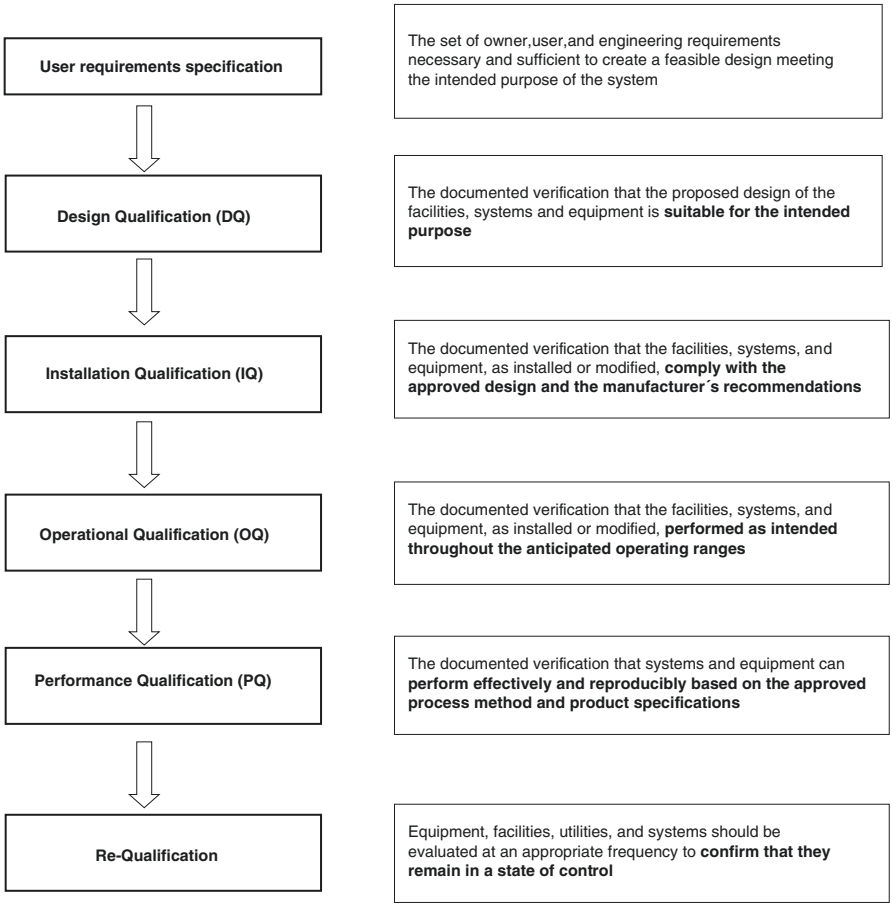

Fig. 5.3 Qualification stages for equipment, facilities, utilities, and systems

Validation tests Based on the validation plan, an adequate number of tests should be performed. The number of tests required to consider the process validated will vary, based on the frequency of the respective activity, level of risk, precision, range of acceptable or expected results, etc. The rationale and the established number of tests should be documented. The validation study should include the parameters to be verified, the expected results, the criteria and acceptance range, and the method for verification (test, visual assessment, document-based, etc.)

Validation review and approval Following completion of the validation, all data analyzed, the output and results should be included in a final validation report; the quality manager and the transplant program director and/or facility director should review the report and confirm with their dated signature that the process is validated and that it may be used for clinical purposes.

Periodic validation The transplant program or facility shall decide on the length of the validation cycle. This decision should be based on various factors, including the level of risk, the internal control process, equipment wear, and other components. The basis for this decision shall be described and documented.

Change control If a significant change is introduced in the process, it should be revalidated. A change control analysis is required before starting the validation study to predict the possible impact of the change on the process (Fig. 5.4).

Example of Documents and Registration Forms for Validation

Validation Master Plan (VMP)

General SOP or other document that describes how to perform a validation study.

Validation Study

A specific SOP or document that describes how to perform validation of a specific process. It contains the specifications of the process (phases, components to be qualified, expected output, prerequisites and performances, type and range of evidence required to confirm that the process is validated).

- Data collection and analysis form
- Qualification form for materials/supplies
- Qualification form for facilities

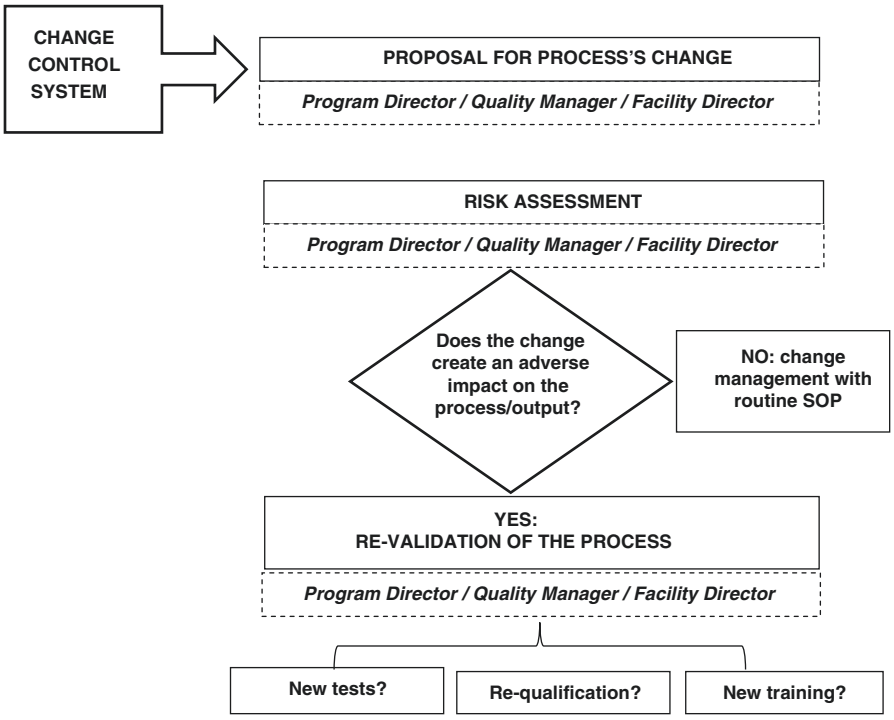

Fig. 5.4 Change control flowchart

- Qualification form for equipment
- Validation final report
- Change control report

Computerized systems used in the manufacture of medicinal products should also be validated according to the requirements of EU-GMP Annex 11; these are not included in this chapter, for details see reference [2].

Glossary

Change Control A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validation status of facilities, systems, equipment, or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Process validation The documented evidence that the process, operated within established parameters, can be performed effectively and reproducibly to

produce a medicinal product/cellular therapy product meeting its predetermined specifications and quality attributes

Qualification The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

Quality assessment The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

Quality assurance The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected or exceed expectations individually and collectively.

Quality risk management A systematic process for the assessment, control, communication, and review of risks to quality across the lifecycle.

Quality Conformity of a product or process with pre-established specifications or standards.

Verification The confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification distinguish from validation in that validation determines that the process performs as expected whereas one verifies that the products of a process meet the required conditions.

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Chapter 6
Outcome Analysis

Anne Emmett

What Is Outcome Analysis?

Outcome analysis does not directly assess the quality of performance, it only allows for interpretation of the quality of the process and structure of care. A set of key performance indicators (KPIs) should be established to 'measure' against.

Outcome analysis can be a subjective process as good outcomes can come from poor care and poor outcomes can come from good care. There are many interplaying factors that need to be considered and a 'one-size-fits-all' approach cannot be established. It is important to ensure that the intended outcome is consistent with the systems and processes put in place by each facility.

Ensure that the intended outcome measure is clearly defined and quantifiable. Ways of measurement can be against a scale, by questionnaires, direct observation, or retrospective review of data.

Policies and procedures should describe in detail the steps to be taken to perform outcome analysis. The process for outcome analysis should follow the PDCA quality cycle processes of Planning (what is going to be analysed), Doing (undertaking the analysis), Check (that what has been done was correct) and Acting (taking action to improve based upon the findings).

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EBMT European Society for Blood and Marrow Transplantation

Standard B1.1.1: The Clinical Program shall demonstrate common staff training, protocols, Standard Operating Procedures, quality management systems, **clinical outcome analyses,** and regular interaction among all clinical sites

Definition:
Outcome analysis: The process by which the results of a therapeutic procedure are formally assessed

Evidence: Regular interaction. Regular interaction means meetings and conferences that are regularly scheduled, multidisciplinary, involve all clinical sites, and are documented in meeting minutes, including documented attendees. Regular interaction should involve physicians, nurses, coordinators, social workers, education consultants, processing staff, collection staff, and others.
This should include regularly scheduled conferences for topics such as morbidity and mortality, quality assessment and improvement, protocol development, journal clubs, patient assessment and evaluation, **patient outcomes,** tumour boards, continuing education presentations, interesting case presentations, etc.
Such topics could also be reported in joint manuscripts or abstracts for national meetings. The inspector should check attendance to confirm that all sites are represented, and that attendance is documented.

Fig. 6.1 Sample standards from v7

Standards

There are 146 incidences of the word 'outcome' or 'outcomes' within the seventh standards, so it is present in many of the standards, or explanations of standards, or evidence required (Fig. 6.1).

As the standards mature, into the eighth, ninth, and tenth standards and beyond, it can be expected that the need to present outcome improvements will become more prevalent, so the ability to document and review these key performance indicators (KPIs) will become more essential.

Collecting Data

When collecting data, be clear to identify which patient groups/subgroups are being included. Data will normally be collated from patient notes/records/care plans.

Outcome analysis, in line with the standards, can be difficult to establish, but the fundamental requirements are arguably quite simple:

- The results of what has taken place should regularly be looked at and reviewed, at least quarterly and ideally more frequently, depending on patient numbers.
- Analysis that MUST be completed: (Table 6.1) (reference JACIE Standard)
  - 100-day mortality
  - Time to engraftment
  - Recipient outcome after infusion of a product with a positive microbial culture

Table 6.1 Sample of data presentation[2]

Discharge Document	Speciality	Month	Hosp No	Last Name	First Name	Date of BMT	No.	Transplant Type	Conditioning	Donor Type	Source	Discharge Date	Life Status	Days to Neutrophil recovery (0.5 x 10^9)	Days to Platelet recovery (20 x 10^9)	Engraftment (% Donor)		CD34 Cell Dose/kg	CD3 Cell dose/kg	TNC/MNC/WCD/kg		100 days	Acute GvHD Grade	Date of Death	Comments
																2/3 weeks	100 days								
Y	Oncology	Nov					1st	HSCT	Bu/Melph	AUTO	PBSC		Alive	12	Never below	–	–	5.00 × 10^6	–	–	–		–		
Y	Immunology	Nov					1st	HSCT	Flu/Treo/Alem	MUD	PBSC		Alive	15	11	100% (7-9-18)	16% (27-11-18)	50.93 × 10^6	7.94 × 10^8	W	33.73 × 10^8		0		
Y	Immunology	Nov					1st	HSCT	Flu/Treo/Alem	MUD	PBSC		Alive	14	14	100% (30-8-18)	100% (9-11-18)	22.01 × 10^6	7.65 × 10^8	W	20.01 × 10^8		0		
Y	Haematology	Nov					1st	HSCT	Flu/Treo/Alem/Thio	MUD	PBSC		Alive	29	12	100% (30-8-18)	100% (14-11-18)	16.71 × 10^6	3.26 × 10^8	W	8.57 × 10^8		0		
N	Haematology	Nov					1st	HSCT	Flu, Theo, Thio, ATG	MMFD	BM		Alive	21	43	100% (24-8-18)	100% (23-10-18)	5.09 × 10^6	0.71 × 10^8	W	7.94 × 10^8		0		
Y	Oncology	Nov					2nd	HSCT	Bu, Mel 140	AUTO	PBSC		Alive	11	52	–	–	3.40 × 10^6	–	–	–		–		

Have outcome data as a standing item on the quality management/clinical governance meeting

Quality indicators include CAR-T/IEC and other novel therapies.

- 100-day mortality
- Acute GVHD grade within one hundred (100) days after transplantation
- Chronic GVHD grade within one (1) year after transplantation
- Engraftment data review
- Late engraftment due to complex issues
- KPI for platelets not met
- Auto recovery data (Table 6.2; Fig. 6.2)
- CAR-T metrics (Table 6.4)
- Apheresis data and any cancellations
- Central venous catheter infections
- Complaints
- Incident reports
  - Labs
  - Wards
  - Outpatients
  - Apheresis
  - Pharmacy, etc.

Table 6.2 Sample of data presentation[2]

Patient	Days to ANC >0.5	Trust Mean	National median	Quality limit	Lower limit	Upper limit	Month of transplant	Date of transplant
Patient 1	10	12	12	21	14	28	Jan-18	01-Jan-18
Patient 2	12	12	12	21	14	28	Jan-18	02-Jan-18
Patient 3	14	12	12	21	14	28	Jan-18	03-Jan-18

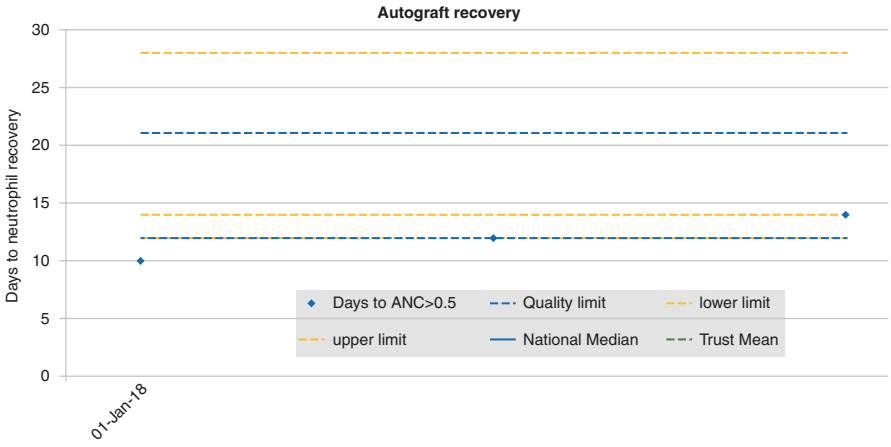

Fig. 6.2 Sample of data presentation [2]

Table 6.3 New KPIs [2]

CAR-T metrics	TRIAL
	ID
	FN
Molecular CR %	SN
TRM[NRM] %	Day 0
	DoD
	Dsch
Alive at [days]	30
	90
	365
Remission status at [days]	30
	90
	365
CD19+ or CD19-	If relapse
LOS [days]	Post-CART day 0
Date of	1st relapse after day 0
Time from day 0	To first relapse
Incidence of	CRS / grade
Incidence of	Neurotoxicity/grade
CAR-T cell	Persistence
PICU admission	Y/N
Grade 3–4 cytopaenias >d30	(Duration/ongoing; not lymphopaenias)
Grade 3–4 infections up to	60 days (duration/ongoing)
B-cell aplasia	(Duration/ongoing)
Need for lg replacement from 90 days	(Duration/ongoing)
Molecular CR at d30	<70%
TRM	>10%
	Notes

Over time a comprehensive tracking system can be established (see Fig. 6.3). To collect data, consider the following:

1. *Title*: ensure this is appropriate and repeatable.
2. *Timeline*: decide on appropriate timeline, given issue being measured, and number of patients/potential occurrences – weekly, monthly, quarterly, annually?
3. *Patients*: be clear to identify which patient groups/subgroups you are including in the data collection.
4. *Information Source*: Specific form extracted from medical records and laboratory. Describe personnel and sections of the programme responsible for this form.
5. *Measurement*: Equipment and analysis used; reporting and recording of the data.

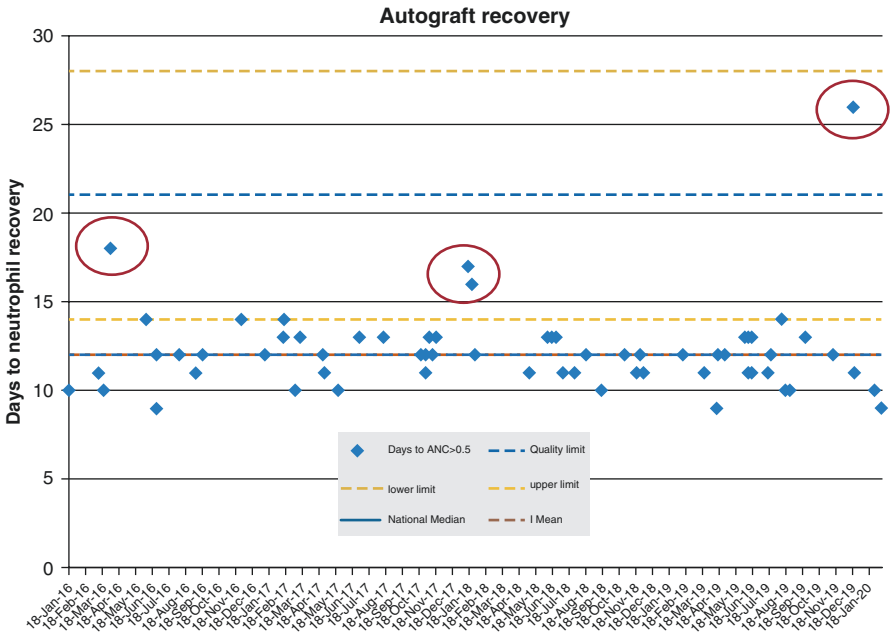

Fig. 6.3 Long-term trending review engraftment [2]

6. *Formula*: if appropriate, ensure consistent formula is used, e.g. number of patients with ANC $\geq 0.5 \times 10^9$/L achieved and sustained for three consecutive days without subsequent decline for ≥3 days.
7. *Definitions*: ensure any definitions are clearly specified, so there cannot be different interpretations.
8. *Adjustment*: make any appropriate adjustments as required, e.g. primary disease, stage at transplant, type of transplant, type of donor or period of transplant.
9. *Assessment Criteria*: There may be several standards to achieve. Minimum acceptable, optimal, or best attainable result.
10. *Related Processes*: If measurement results indicate poor outcome, consider what problems in the process might have made them happen. Was the process done correctly, were there adequate staff in place, did everyone have training?
11. *References Used*: EBMT MED-A/B forms, patient registry, national/international standards, etc.
12. *Presentation*: Report presented and oral presentation at appropriate review meeting.
13. *Observations*: What were the findings that came out of the analysis and what does research suggest might happen to make the results appear as they have – e.g. co-morbidities, age or ethnicity implications

Holistic outcome analysis can also be completed; these tend to be more subjective and completed via questionnaires or interview. Ideally these should have a

process for scoring to facilitate analysis, for example using a scale of 1–10 for pain and satisfaction with ward facilities.

- Quality of life post-transplant
- Late effects (fertility, etc.)
- Satisfaction with care

Staff-based outcome analysis can be completed by establishing a suitable internal level of completion and then assessing the following:

- Quality of information in case notes, paper or electronic, and the effect on day-to-day care structure
- Annual training, education and competency assessment for all staff groups
- Induction of new staff and their understanding of and participation in the quality programme
- Use of drugs and therapeutics against protocols

Establishing Outcome Analysis for Novel Applications

As each new development comes into implementation in the clinical environment, a new set of outcome analysis needs to be developed. One of the more recent of these is CAR-T/IEC. In development with the manufacturer, a new set of KPIs was developed (Table 6.3) and is being monitored as part of 'business as usual'. Once sufficient data has been gathered, the most indicative KPIs can then be used and the remainder used for audit purposes.

Reviewing Data

Outcome reviews should be completed with a wide range of staff and at regular intervals. It is a JACIE standard B/C/D 4.17 (seventh Standards) that the programme director, or designee, shall review and report to staff quality management activities, at a minimum, quarterly (Table 6.4). This presents a local snapshot of activity.

The director shall annually review the effectiveness (outcomes) of the quality management program. An annual report is required by JACIE – so combine the two.

Whilst these are useful, it is critical to look at long-term trending when reviewing outcome data. A failure to do this can result in critical trends not being spotted.

This clearly shows outliers that can be investigated.

It could be 'assumed' from Fig. 6.4 that treatments should not take place in February as two out of 3 years show high pre 100-day mortality. However, a greater depth of investigation is required to determine the causes of this.

As with all reviews, a thorough investigation should take place of any outliers.

Reviews can take the form of [1]:

Table 6.4 Sample of quality summary report [2]

BMT and cell therapy lab QM meetings held	Oct, Nov, Dec
100-day mortality: Patients reviewed Outliers discussed	16 2
Engraftment data review: Outliers discussed	No outliers
Central venous catheter infection: Line days Rate per 100 line days YTD (Apl 2017 – Mar 2018)	872 1.2
Documents clinical: Reviewed and reissued Updated New	9 24 9
Documents laboratory: Reviewed and reissued Updated New	19 4 0
Audits performed: Clinical Laboratory	3 1
Audits presented:	3
Apheresis: Patients % target collections reached	10 90
Leucopheresis: Patients % target collections reached	4 100
CAR T therapy patients reviewed Outliers discussed	2 0

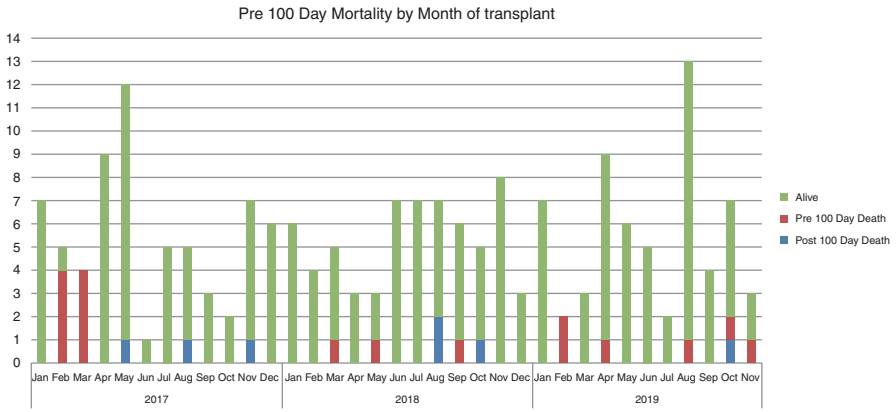

Fig. 6.4 Long-term review mortality [2]

- Details of the processes you are trying to improve
- Details of the areas where these processes take place, i.e. clinical unit, collection facility and processing
- Details of the numbers of staff involved in the processes and who is responsible for which part of the process
- Details of any documentation in place to support the current process, i.e. policies and standard operating procedures

- The actions required to improve the process, e.g.:
  - Simple action – development of patient guide and other information as suggested from patient survey
  - More complex – such as revalidation of stem cell machine or discussion with supplier re-ongoing breakdown problems
  - Testing of machine against several components
  - Changes to donor clearance forms at registry totally in your control
- Details of who is responsible for the actions
- Dates when actions should be completed
- Details of expected outcomes
- Review of actions and outcomes

- Record it
- Review it
- Record review
- Act on it
- Record actions

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Chapter 7
Personnel Requirements Including Job Descriptions

Songul Tepebasi and Ilknur Kozanoglu

Introductıon

Workforce is central to safe and effective delivery of cellular therapy. Staff organisation and collaboration are essential for successful outcomes [1]. It is important to define the roles of key personnel and their support personnel, thus ensuring that tasks are uninterrupted. The number of personnel should be determined in accordance with demand, as well as the nature of the respective centre's activity. Cellular therapies are unique, in that they require many personnel with varying qualifications and competencies to work as a team. For these therapy centres to achieve their goals, employees must work together harmoniously; this requires communication and collaboration among employees [2].

To establish mutual understanding and cooperation between components of hematopoietic stem cell transplantation (HSCT) programs, it is imperative to establish a centralised and active communication network. Motivation is another factor that ensures effective and efficient employees. Training, organisation, management, and development of personnel should all be prioritised within the quality management plan, alongside regulations that ensure the occupational safety and health of workers for all processes [2–5].

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Organisational Structure and Organisational Chart

The organisational structure is a coordination system that enables individuals to realise their goals by combining their respective efforts, knowledge and abilities through collaborating with others, as well as through development and execution of a structure considered most suitable to achieve a specific goal. While developing the organisational structure in cellular therapy centres, the hierarchy, collaboration and communication of all units both within and outside the centre must be easily understood [3–5].

The organisational chart should define, maintain and work with the optimal number of staff in the quality management system. Each level in the chart should consider the tasks, capabilities, responsibilities, and communication networks shaped within the framework of business processes and corporate systems. The scheme should reflect quality management, along with clearly defining the roles, authority, responsibilities and duties of all employees [3–5].

In centres that provide cellular therapy services, organisational charts should never be made for individuals; they should be developed for units as a whole. This includes the organisational structure of all units involved, such as clinical units, cell processing, peripheral blood or bone marrow collection units, other disciplines (e.g., consultants), supporting units (e.g., medical/nutritionist) and administrative units (e.g., transportation unit and housekeeping), alongside all units with a service level agreement. Organisational charts should be developed in accordance with targets, systems and processes; staff should be chosen for positions within the chart, based on their qualifications, competencies and training. This is necessary, as the performance of a centre is directly influenced by its organisational structure [3–5].

The quality management system should be able to accommodate fluctuations in personnel and cover planned and unplanned unavailability to maintain operations on a day-to-day basis, e.g. illness, annual leave and departures [1–5]. Succession planning for key position should also be considered, e.g. quality manager (1). Education, quality and motivation of personnel are the most important factors for ensuring well-organised human resources and quality awareness within cellular therapy centres.

Key Personnel

All personnel involved in the planning, management and control of critical activities, both directly and indirectly, in the field of cellular therapies should be defined as key personnel. For example, these personnel would include individuals performing stem cell collection, processing and freezing procedures. This definition will determine in advance when and what individual cellular therapy centres can provide, along with the personnel available within the centres.

It is necessary to ensure that personnel designated and appointed conform to the requirements and qualifications of the job to be undertaken. In addition, the experience and abilities of individuals should be considered during the selection; those selected should be trained in accordance with their duties. Designated key personnel should remain unchanged wherever possible; supervisors of key personnel should be trained to an equivalent standard, such that where key personnel are not available, those supervisors may step into the role as necessary [3–6].

Personnel Competency

Haematopoietic cellular therapies have complex and dynamic treatment pathways. All employees working in the field of cellular therapy should therefore be developing and improving skills and knowledge through continuous training [6]. As such, competencies of employees should be measured and recorded regularly within the quality management plan (Standards B3, C3, CM3, D3) [5]. The ability of employees to work effectively provides an indicator of the quality of training, its relevance to the requirements of employees in their respective roles and whether the system is working correctly with expected results. Various methods can be used to measure the adequacy of employees for a given role. A table completed through measurement or observation can be used; electrical monitoring systems can also be used (Table 7.1).

Responsibility and Task Awareness

Once recruited, personnel are given powers and responsibilities required to perform in their given roles. Individuals must know and understand their role, to whom and to what extent they have authority, and to what extent they can give instructions to others who rely on them. To achieve this, job descriptions should include relevant duties, necessary qualifications, responsibilities and authority.

Use of Effective Communication

Cellular therapy centres function as a multidisciplinary unit with other components within the same hospital and/or program, as well as with other centres both inside and outside of the country. To achieve this objective, interaction, cooperation between units and a common language are proven elements for success in the field. It is vital for all personnel involved in the process to possess good communication skills and be able to use communication resources effectively. Communication meetings with all personnel and key personnel involved in the processes should be

Table 7.1 Sample personnel performance form

Example of personnel competency evaluation form	
Evaluated employee: Name and surname: Unit of work: Start date of work:	Evaluator (director/supervisor) Name and surname: Signature: Date: Score:
1	Adherence to both written and verbal communication standards of the institution (including compliance with working hours and dress code)
2	Knowledge, adoption and implementation of institution's quality policy and objectives
3	Identification of business priorities, including effective use of time and resources
4	Communication and collaboration with superiors and other team members
5	Adherence to patient, donor, product and occupational safety rules
6	Collaboration with others in tasks requiring teamwork, providing support and meeting deadlines
7	Possession of effective communication skills; protection of confidentiality for patient donors and medical records
8	Willingness to undergo further training and self-development
9	Attention to detail; timely recognition and resolution of problems
10	Comprehension of working role; ability to perform appropriately; leadership potential
Total score (all questions scaled from 1 to 10): 0–20: Very unsuccessful; 21–30: unsuccessful; 31–60: moderately successful; 61–80: successful; 81–100: very successful	
Employee strengths:	
Employee weaknesses:	

scheduled regularly. These multi-unit meetings should be recorded and presented within annual reports [3–5].

All personnel should undergo annual appraisal of performance and other key aspects of their work and relationships with others in the team, with appropriate action taken in order to promote team work and good practice and maximise quality for product safety and, ultimately, patient and donor benefit [7–8].

Job Descriptions

The roles of personnel included in the organisational chart of cellular therapy centres must be clearly defined in advance. Processes within cellular therapy centres are complex; as such, any errors that may occur must be minimised. Accordingly, European Union Directive 2006/86/EC states that all personnel working in the field

of cellular therapies should have clear, documented and up-to-date job descriptions; moreover, their duties and responsibilities should be clearly documented and understandable [9].

International standards also require that current job descriptions be documented within the audits and that employees have received training for their respective job descriptions [5]. If employees have been given responsibility for a critical procedure, they must possess sufficient competencies to fulfil this responsibility. In addition, the level of authority should not be less than or greater than that required for the responsibility; the task designation of the employee should be sufficiently detailed in the job description. This should detail the positions of employees within the organisational chart [3–5].

Job descriptions must be written, understandable, and clear. When employees read their job descriptions, they should not have to guess or interpret meanings beyond those which are written. Job descriptions should be concise, define the current position and possess a dynamic structure. They should not restrict the employees in their tasks, but should allow the employees' experience to inform the work that each member performs. While creating a job definition, it is necessary to determine the nature of the proposed task and who will write the task description. The author should be competent and knowledgeable regarding the task and how it will function. When the definition of the task is initially formed, ideas should be collected from employees by means of interview or survey. It may also be useful to examine job descriptions created for similar positions in other institutions [10].

When a job definition is created, it should be properly documented. All job descriptions should be reviewed and approved by the relevant centre or unit director. The director should convey the final definition of the task to the relevant personnel; the relevant personnel should then be trained accordingly. The personnel must be confirmed to fully understand the content of the job description. An examination, observation or similar method can be used for this confirmation [10].

The structure of the job description may vary among centres; however, all job descriptions within an organisation should have a standardised appearance [10].

The following topics should be included:

- *Job title* – name of the position.
- *Salary grade/level/range* – compensation levels, groups or pay ranges, into which jobs of the same or similar worth are placed, including minimum and maximum pay bands.
- *Reports to* – title of the position this job reports to.
- *Date* – date when the job description was written or last reviewed.
- *Summary/objective* – summary and overall objectives of the job.
- *Essential functions* – essential functions, including how an individual is to perform them and the frequency with which the tasks are performed; the tasks must be part of the job function and be required to perform the job.
- *Competency* – knowledge, skills and abilities.
- *Supervisory responsibilities* – direct reports, if any, and the level of supervision.

- *Work environment* – the work environment; temperature, noise level, inside or outside, or other factors that will affect the person's working conditions while performing the job.
- *Physical demands* – the physical demands of the job, including bending, sitting, lifting and driving.
- *Position type and expected hours of work* – full time or part time, typical work hours and shifts, days of week and whether overtime is expected.
- *Required education and experience* – required education and experience based on job-related requirements and consistent with the requirements of the centre.
- *Preferred education and experience* – preferred education and experience based on job-related requirements and consistent with requirements of the centre.
- *Additional eligibility qualifications* – additional requirements such as certifications, cellular therapy–specific experience and experience working with specific items of equipment.
- *Other duties* –.

Signature lines Signatures are important in validating the job description. They indicate that the job description has been approved and that the employee understands the requirements, essential functions and duties of the position. Signatures should include those of the supervisor and of the employee [10].

Personnel File

Personnel files should be created for uninterrupted monitoring of all key personnel in the quality management system. When no longer required, these files should be archived in a secure area for the period specified in the quality plan. Personnel files are confidential and should therefore be kept with controlled access. These files include personal education information, training participation and personnel qualification evaluations. Related documents should be included; when the employee leaves the unit, their file should be retained [3–5].

Conclusion

An important responsibility of directors working in cellular therapy centres is to understand and define the roles and responsibilities of employees so that their objectives are best met. This enables directors to better distribute workload to personnel appropriately, whilst maintaining safety and efficiency. The collection of personnel or staff satisfaction surveys at regular intervals is recommended. The results should be evaluated at the quality committee meetings or similar groups with the goal of optimising ongoing processes and operations as well as workforce well-being.

A continuously improving quality management system incorporating the correct personnel with clear roles, responsibilities, training, competency and working relationships will ensure that processes are effective and efficient and maintain safety and quality for the programme. Processes are numerous and diverse; personnel should have continuous development of skills and qualifications, and key personnel should continuously contribute to the training, competency and personal development of new and existing personnel. Continuity and robustness of operations should be supported by cross-cover arrangements and succession planning. All of these aspects are covered by FACT-JACIE standards and the accreditation process, which should be used as an opportunity to review personnel and their functions, and, where necessary, identify deficiencies or weaknesses, undertake corrective actions or highlight issues to the accreditation organisation and external inspectors during the accreditation process.

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Chapter 8
Third-Party Agreements

Anne Emmett

Gentlemen's Agreement

In the past, many issues were resolved following discussion and a handshake between two parties (Fig. 8.1). Nothing was written down and progress depended on continued verbal agreement. In some cases, the reason for the original agreement is lost and things just 'carry on'. This is NOT acceptable within JACIE, nor any professional environment.

Memoranda of Understanding (MoU) [1]

This is a more formal written arrangement between two, or more, parties. It may take the format of a completed form with basic information, or may just be a formal letter, but would be signed by both parties.

A MoU (Table 8.1) can be the first step in establishing a process or partnership. However, MoUs are not legally binding and so cannot be deemed to be a suitable process for maintaining services between parties. They do indicate a degree of seriousness and mutual respect. They imply that a formal written contract, agreement – either technical or third party – or a service-level agreement is to follow.

A MoU can be assessed as a 'first step' towards a formal agreement. It can be terminated without legal consequence in most circumstances.

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Fig. 8.1 Gentleman's Agreement

Table 8.1 Outline of MoU

Name of contracting organisation:	Address:
Designated contact person:	
Name of third party:	Address:
Designated contact person:	
Activity/activities MoU covers:	
E.g. • Procurement • Testing • Processing • Distribution • Export • Supplies goods or services that affect quality or safety	
Reference to protocols and SOPs to be followed to meet the required performance specification (attach copies)	
Where applicable, reference to control measures or audits to be carried out by the contracting organisation and which the third party agrees to support (e.g. on-site audit at specified intervals and audit of reports to be provided by third party)	
Reference to reporting requirements of the third party to the contracting organisation	
Reference to systems for managing adverse events and incidents	
Date on which the agreement will be reviewed:	
Details of the person with responsibility to review the agreement:	
Signed: Contracting organisation	Date:
Signed: Third party:	Date:

Fig. 8.2 Contract

Contract/Commercial Agreement (Fig. 8.2)

A contract is the main document governing the deal between you and another organisation. It is the written formal agreement between the two parties. It stipulates each party's legal responsibilities, obligations, governance, contract length, financial details and liabilities within the agreement. It will include the commercial agreements and does not go into the purely technical aspects of the manufacturing, supply or outsourcing of the product or process (Table 8.2). Where possible, sections should not be reproduced in multiple documents, as this can lead to contradictions and conflicts. Where appropriate, cross references to relevant sections in different documents should be made.

As such, it is typically drafted by the legal, financial and management teams of the contractual parties.

Service-Level Agreements (SLAs)

An SLA focuses on measuring performance and quality, as agreed between you and another organisation. The SLA should not determine governance arrangements, financial arrangements, contract lengths, etc. (see Contract section), though these are often incorrectly included in SLAs, making the SLA very long and overcomplicated.

Creating an SLA as well as a contract allows you to revise the SLA without changing the contract. Though the contract may be for 5 years, the SLA may be reviewed and amended as frequently as required and at least every 2 years for JACIE.

The SLA (Table 8.3) should include a description of the services to be provided and their expected service levels, metrics or key performance indicators (KPIs) by which the services are measured, the duties and responsibilities of each party, the remedies or penalties for breach, process for disagreements and a protocol for adding and removing metrics.

Table 8.2 Typical contract contents

1.	Definitions and interpretation
2.	Contract period
3.	Services
4.	Service amendments
5.	Contract price
6.	Charges and terms of payment
7.	Warranties and representations
8.	Intellectual property
9.	Liability
10.	Quality and safety standards
11.	Freedom of information
12.	Confidentiality
13.	Data protection act
14.	Information security
15.	Force majeure
16.	Assignment
17.	Contracts (rights of third parties)
18.	Complaints
19.	Authorised officers
20.	Health and safety
21.	Publicity
22.	Prohibited acts
23.	The prevention of fraud
24.	Notices
25.	Satutory invalidity and severability
26.	Audit requirements
27.	Law and jurisdiction
Schedule 1	Authorised officers
Schedule 2	Charging structure
Schedule 3	Prices

Table 8.3 Typical SLA contents

1.	Definitions and interpretation
2.	Named contacts and responsibilities
3.	Services being provided and key performance indicators
4.	Service amendments and variations, including metrics
5.	Quality and safety standards
6.	Termination
7.	Consequences of termination
8.	Dispute resolution

Technical Agreement

A technical agreement (Fig. 8.3) (also known as a quality agreement) is a written contract that is required whenever you outsource an activity covered by quality guidelines – often good manufacturing practice (GMP) guidelines for pharmaceutical products, but equally JACIE, HTA, FACT and other national and international quality standards. It sets out the quality management responsibilities of each of the parties, both quality control and quality assurance (Table 8.4).

Even though there is an outsourcing of a process, the organisation contracting the process is still accountable for outcomes and is therefore responsible for the activities of the contracted organization. Make sure there is involvement in change control, including assurance that any appropriate validation and qualification are carried out and documented; that there is involvement in any major or critical investigations, and in any other critical issues that require both parties' input; and ensure that the level of involvement is detailed in the Technical Agreement. The contracting organisation needs to also define how often there will be audits, or audits requested, and if it is intended to send in an independent auditor; this too needs to be specified.

Fig. 8.3 Technical agreement

Table 8.4 Typical technical agreement

1.	Definitions and interpretation
2.	Named contacts and responsibilities
3.	Services being provided
4.	Service amendments
5.	Accessing service(s)
6.	Quality and safety standards responsibilities
7.	Policies, procedures and documentation responsibilities
8.	Information security responsibilities
9.	Health and safety responsibilities
10.	Incident and risks responsibilities
11.	Audit requirements and responsibilities

The technical agreement spells out the *technical specifications and responsibilities* of the parties required for the technical or outsourcing activities and processes. It is to ensure compliance with various QC (quality control) and QA (quality assurance) requirements of the technical process or the outsourcing [2].

It is typically drafted by the technical teams in each organization. It is not usually necessary to get legal advice on a technical agreement because a lawyer will not usually be able to advise on the actual details of a technical agreement.

Third-Party Agreement

Third-party contracts are agreements that involve a person who is not a party to the contract but is involved with the transaction. This could, for example, be that an organisation is contracted to carry out viral analysis in which case the organisation will then contract the staff to do the work. The staff completing the viral analysis have not directly signed the contract but are involved with the transaction. This can get very confusing within the clinical environment if the staff doing the work also have honorary, or permanent, contracts with the contracting organisation.

Quick Checklist [2]

The contract should always refer to the technical agreement for technical matters related to quality control and assurance. As such, the technical agreement should not contain "legal" or "commercial" terminology.

No duplication of provisions should relate to the same subject matter, so that one document simply refers to the relevant provisions in the other document, i.e. instead of repeating or restating the same thing. This is to avoid accidental conflicts or contradictions.

There should be consistency in nomenclature, definitions, and duration such as the same name of the parties in both documents, the same process, the same definitions for terminology and expressions, and the same duration of each agreement.

There should be no "legal" or "commercial" terms in the technical agreement. The job of the technical agreement is to set out technical parameters. It is not intended to set out the commercial relationship between the parties that should go into the contract instead.

That means that the contract is the right place to cover things like patient confidentiality terms, warranties, indemnities, liability limitations, pricing, scheduling, etc.

Fig. 8.4 Communication

Communication Is Critical [3] (Fig. 8.4)

Define:

- Who
- When
- What
- Where
- Why

Make sure that the contacts are clear to both parties and that their communication channels are open.

Ensure there are nominated single points of contact in each organisation for key matters, plus 'local' contacts as required, e.g. HTA lead, quality manager, service manager, accounts. Ensure that, where necessary, there are secure email connections, or use encryption for any emails containing personal or patient data. Ensure this is made clear in all joint documents.

Try to avoid 'scatter gun' communications between the organisations when setting up the agreement and then running the process as this can lead to either key communications being lost or email overload. When necessary, have face-to-face meetings, even if this is by video conference.

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Chapter 9
Performance Measurement

Amal Alseraihy, Waleed Rasheed, and Mahmoud Aljurf

Accountability and performance are vital pillars in healthcare organizations as both are key factors on the platform of global initiatives in healthcare and monitored through the management of performance measurements. In the context of rising healthcare expenditure, performance measurement (PM) is becoming increasingly integral to accountability. Healthcare accountability mechanisms have traditionally included business planning, annual reporting, and contracting. In recent years, a richer sense of accountability has emphasized the achievement of goals effectively and efficiently and has stimulated the growth of PM. PM has been described as "the use of statistical evidence to determine progress towards specific defined organizational objectives" (State of California 2003) [1]. The literature includes reports on performance measurement initiatives across the healthcare spectrum from primary through tertiary health care and public health and the voluntary sector, many driven by the backend as a reactive response to demands from governments, consumers, other payers, proponents of evidence-based practice, and accreditation organizations [2]. Substantial resources, by various organizations, have been invested in PM system development from policy level to front-line care delivery.

Performance measurement (PM) in its simplest form is the "measurement of performance": the regular and continuous assessment of whether the current processes or practices in place are accomplishing the goals and objectives created, implemented, and monitored to sustain the organization, company, or program" [3].

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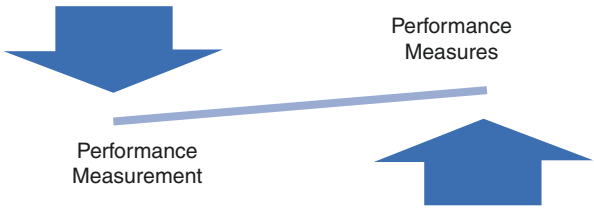

Fig. 9.1 Performance measures versus performance measurement

Utilizing well defined measures will promote a culture of continuous growth and development, both clinically and operationally. Such necessity for PMs is the same for a stem cell transplant program – to ascertain and continuously monitor processes that function within the program from financial to operational to clinical aspects. PM is the process and performance measures are the drivers used to establish the level of success or need for improvement (Fig. 9.1).

SCT is a highly specialized and cost-driving service, operating at multiple levels of structures and processes, according to each program's capacity and complexity of treated cases. Whether the focus of the program is to achieve excellence or to build a quality system or to comply with national or international accreditation, performance improvement and management can be challenging for the decision makers without objective customized performance measures for such complex medical care. The first part of this chapter will provide the reader with a comprehensive review of performance measurement definitions, development, and working framework. The second part will focus on performance measurement in SCT program.

Definitions for Healthcare Performance Measurement

Performance measurement In general terms, it can be defined as the regular measurement of outcomes and results, which generate reliable data on the effectiveness and efficiency of various aspects of an organization that keep it afloat.

Input Resources (human resources, employee time, funding) used to conduct activities and provide services.

Activity Individual tasks funded by projects or programs.

Output Products and services delivered. Output information does not tell you anything about the actual results achieved or the consequences of the products and services delivered. Output information is important to show the scope or size of what the inputs and activities produce.

Outcome An outcome represents a specific result a program is intended to achieve. An outcome can also be defined as the specific objective of a specific program or

service. An outcome is not what the program produced itself (the output), but the consequences of those products, services, or assistance. It is important to distinguish between end outcomes (objectives), on one hand, and intermediate outcomes (intermediate results), on the other.

End outcomes (objectives) This is the highest-level objective toward which a program works. The end outcome is what the program is designed to ultimately achieve: which should be the most "ambitious" outcome or result program managers can materially affect or influence and for which they are willing to be held responsible.

Intermediate outcomes (intermediate results) An intermediate outcome or intermediate result is a critical outcome or result that must occur in order to reach the higher-level, end outcome/objective. As the PM process advances, it is important to understand the necessity to obtain and act on the intermediate outcome or result before achieving the end outcome/objective.

Indicators An indicator is an instrument that helps you measure change over time. It is important to remember that end outcomes and higher-level objectives require higher-level indicators. Intermediate outcomes/results require lower-level indicators. Indicators can be quantitative, or qualitative, or a hybrid of the two.

Performance indicator or key performance indicator (KPI) A quantifiable measure used to evaluate the success of an organization, employee, etc., in meeting objectives for performance.

Measure Development Life Cycle

Figure 9.2 illustrates the five phases in measure development life cycle. Although the life cycle shows each phase as a discrete activity, the measure life cycle is dynamic. Some phases may overlap or take place concurrently or result in feedback with earlier phases [4].

Conceptualization Develop measure concepts and then narrow down to specific measures. The developer conducts an environmental scan and requests input from a broad group of stakeholders, including patients.

Specification Identify the population, the recommended practice, the expected outcome, and determine how it will be measured.

Testing Assess the suitability of the quality measure's technical specifications and acquire empirical evidence to help assess the strengths and weaknesses of a measure.

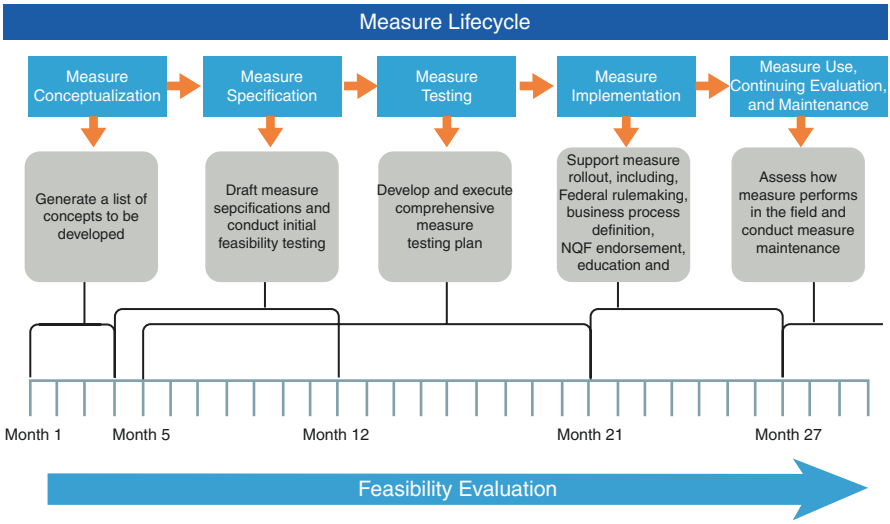

Fig. 9.2 Example for performance measure life cycle; https://www.cms.gov/Medicare/Quality

Implementation Identify measures to submit for selection and rollout processes.

Use, continuing evaluation, and maintenance Ensure that the measure continues to add value to quality reporting measurement programs and that its construction continues to be sound.

The Centers for Medicare & Medicaid Services (CMS) uses the following decision criteria throughout the measure development cycle to ensure that a measure meets the applicable standards before moving to the next phase:

Importance to measure and report including analysis of opportunities for improvement such as reducing variability in comparison groups or disparities in healthcare related to race, ethnicity, age, or other classifications.

Scientific acceptability including analysis of reliability, validity, and exclusion appropriateness.

Feasibility including evaluation of reported costs or perceived burden, frequency of missing data, and description of data availability.

Usability including planned analyses to demonstrate that the measure is meaningful and useful to the target.

Measure Development Process

Bringing It All Together

As previously stated, in this chapter, performance measurements for stem cell transplant programs operate, as they do, in general with all standard healthcare organizations, ensuring that all indicators and measures directly link to the organizations' strategic objectives, mission, and vision statement – utilizing key performance indicators and the approach of Donabedian's three domain quality framework of structure, process, and outcome measures [5]. Such is the case when conceptualizing the framework to construct, pilot, implement, and monitor stem cell transplant performance measures, ensuring that the critical key performance indicators that are essential to your operational strategic plan and also drive your measures.

Before one can create and implement measures or indicators, you should determine who your key stakeholders and process owners are as this is as important in determining your measures/indicators. These are those individuals who will work to bring to fruition your desired outcomes after you perform your intense education sessions with them and to provide the knowledge and training needed to meet the target set for your measures or indicators.

To begin with each measure or indicator is intentionally chosen through the process of conducting an RCA (Research, Compare, & Act), which begins with a rigorous internal research to determine specific programmatic needs, performing external literature reviews to determine best practice, and applying your finding in research to compare your current state with the desired state (Fig. 9.3).

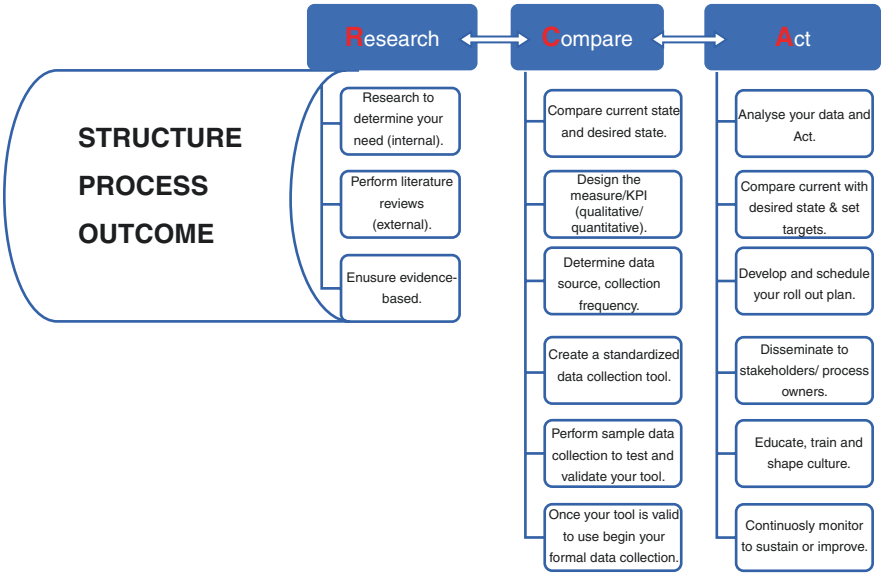

Fig. 9.3 SCT performance measurement RCA framework

Once you have accomplished your research, compared your findings, determined what you need, your team is now ready to agree on the design of the selected qualitative and/or quantitative measure/indicator, determine your data source and collection frequency, create and validate a standardized data collection tool and perform a sample collection to test your tool. If the data tool collects what you designed and desired, perform a real data collection session. If not, go back to the drawing board, assess your tool, determine the cause, and make the revisions, as needed. You will not be able to move forward until your data collection tool is considered valid and confirmed as effective to collect the data it was designed to collect. Once you have collected your data, you are now you ready to Act: bring the outcome of your arduous work to action by performing an analysis on your data. Once your data has been analyzed and your targets set based on your current and desired state, you are now ready to develop your roll-out plan and schedule your action. First, disseminate your findings to your stakeholders and process owners to get them ready for your upcoming education and training sessions. A well-informed team is a well-equipped team and ready to assist you to shape the culture for success. It is now time to perform your educational sessions indicating your findings, beginning with the RCA, propose the plan to move forward and ensure to involve your team in continuous monitoring by setting champions in each area. If you have obtained your goal you will need to sustain the gain. If improvement is needed, use your well-informed team champion to perform continuous monitoring, education, and training until desired outcome is achieved.

As you now have set your data collection schedule, you will need to adhere to this to ensure continued success. Create dashboards or scorecards (Tables 9.3 and 9.4) to maintain intentional active continuous monitoring, allowing you to promptly act to any measure or indicator that may fall beyond the set target.

Performance Score

In most cases, at its basic level, a performance measure is a ratio. The denominator represents the number of eligible cases, less any exclusions or exceptions, and the numerator represents the number of instances the clinical action of interest was performed. It is helpful to note that the denominator is often derived from, and sometimes equal to, an initial population; this initial population is the broadest grouping (e.g., all patients age 14+ with transplanted specified diagnosis). The initial population can be reduced to a denominator (e.g., all

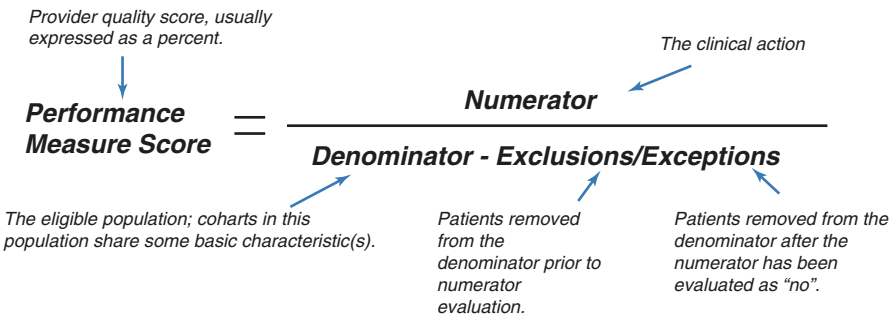

Fig. 9.4 Anatomy of a performance measure

initial population patients that underwent transplant) and then to a denominator with exclusions and exceptions removed. Figure 9.4 below visually depicts the anatomy of a performance measure from an arithmetic perspective.

Goals for Measure Development in SCT Program

A critical aim of any stem cell transplant center or program is to ensure that such measures are directly aligned with the mission and vision statement of the healthcare organization in which it dwells. In addition, safeguarding the process within performance measurement affords one the ability to assess the current state, benchmark with competitors, ensure continuous assessment for improvement opportunities, ensure accrediting governing body's continuous readiness, and monitor growth and development: internal assessment for an external cause corporately and publicly. Some challenges with PM in SCT can be the substantial variations in SCT center characteristics; centers have different care models to optimize the use of available resources, identifying external benchmarks and utility of comparative external benchmarks. However, the primary purpose of quality measurement is to identify opportunities to measure and thus improve patient care and other program-related outcomes. Table 9.1 summarizes some guiding principles for measure development.

Quality measure development remains a focus for quality assurance and value staff to continually meet the evolving needs of its members, help its members meet national and international accreditation requirements, and to provide members with information that informs clinical decision–making.

Table 9.1 Criteria for performance measures selection [2]

Criterion	Description
Evidence based	Defines measures that are valid and reliable with operational definitions that have already been proven through rigorous research
Strategic	The measure directs attention toward the ultimate change desired
Important	The measure addresses an important or serious health or health services problem (usually defined as health burden or cost) such that there will be sufficient impact from collection and service improvement initiatives
Attributable	Causal links between the measure, service improvements, and health outcomes are known
Actionable	Defines a measure that addresses a service area that can benefit from an improvement
Feasible	Data collection, reporting, and follow-through are cost-effective (potential benefits outweigh costs) and there is reasonable technical capacity for collection and analysis, including risk adjustment of compared measures
Relevant and meaningful	The measure is relevant to most stakeholders, including policy-makers, managers, clinicians, and the public
Understandable	The measure is understandable to a non-technical audience (often just a communication issue)
Balanced	The set of measures is balanced across types of treatments, treatment settings, major health problems, age groups, special populations, and levels of the healthcare system. The set is balanced across short- and long-term measures, and balance and appropriateness are considered across process- and outcome-type measures
Responsive	The measure is sensitive to change over time
Robustness	Potential adverse effects of the measure can be mitigated, and vulnerability to gaming is minimal
Non-ambiguous	The measure is clear in terms of which direction for service change is desirable

SCT Program Performance Measure

There are several types of performance measures, but structural, process, and outcome performance measures are the most practical and objective that can be implemented in SCT across its three dimensions: clinical, collection, and processing. Table 9.2 outlines some of these performance measures, their definitions, and examples for their indicators in SCT program.

Structural measure Structure of care is a feature of a healthcare organization or clinician related to the capacity to provide high-quality healthcare. Structure measures are supported by evidence that an association exists between the measure and one of the other quality domains.

Process measure A process of care is a healthcare-related activity performed for, on behalf of, or by a patient. Process measures are supported by evidence that the clinical process, which is the focus of the measure, has led to improved outcomes. These measures are calculated using patients eligible for a service in the denominator and the patients who either do or do not receive the service in the numerator.

Table 9.2 Example of performance measures and indicators in SCT

Types of measures	Clinical indicator	Collection indicator	Processing indicator
Structural	Number of SCT-certified physician Number of SCT-certified nurses Number of oncology certified nurses Patient volume Number of publications Bed capacity Average length of stay Supplies and equipment Access to HCT program	Number of trained stem cell collection apheresis staff	Number of allogeneic products Number of autologous products Number of trained cell processing staff Number of publications
Process	Number of discharges by noon Number of stem cell infusion cancellations Staff satisfaction Number of medication errors HCT clinic wait time	Complications during collection procedure Quality of collected product (CD34 quantitation)	SC processing turnaround time Number of acceptable HPC viability cells post-cryopreservation Number of available SC processing reagents
Outcome	Readmission rate 1-Year survival rate Day 100 mortality Engraftment outcome Wrong surgery time Surgical site infections Graft failure outcome Patient satisfaction Number of HCT patient ED visits	Percentage of microbial contaminations Number of donor/patient who are eligible for apheresis	Percentage of microbial contaminations

Outcome measure An outcome of care is a health state of a patient resulting from healthcare. Outcome measures are supported by evidence that the measure has been used to detect the impact of one or more clinical interventions. Measures in this domain are attributable to antecedent healthcare and should include provisions for risk adjustment. The outcome of performance measurement processes should result in improved value. Value in the part of health care domains:

Improved patient care Outcomes (lifestyle and survival)
Improved staff satisfaction Processes and practices
Improved efficiency Improved throughput, capacity, and quality of care and decreased cost
Improved competitive edge Increased marketability and benchmarking
Improved resource utilization Lowering cost (care and product services)

Table 9.3 Sample of annual operational dashboard

KPI	FY	FY	FY	FY
Volume (productivity)				
Number of transplants				
New patient visits				
Return patient visits				
Admissions				
Discharges				
Nurse: patient ratio				
Quality				
Number of adverse occurrence				
Medication error				
Number of patients admitted to intensive care				
100-Day mortality				
Readmission 7 days post-discharge				
Financial ($)				
Revenue per patient				
Labor cost per patient				
RVU per SCT consultant				
Patient satisfaction (%)				
Physician				
Nurse				
Case manager				
Clinic wait time				
Number of patient' complaint				

Performance Measurement and KPI

In its simplest form, a key performance indicator (KPI) is a type of performance measurement (PM); these are the critical (key) indicators of progress toward an intended result. KPIs provide a focus for strategic and operational improvement, create an analytical basis for decision-making, and help focus attention on what matters most.

Goals of an organization should set the focus of your quality, productivity, and financial metrics. The term "metric" means the same as a KPI to some, but to others, it means a collection of related measures that when placed together become a metric. Some have used metrics and KPIs for staffing needs, position justifications, quality assurance, revenue cycle, and strategic planning in various hematopoietic cellular therapy (HCT) programs. Various challenges discovered in implementing a PM within HCT programs are due to the substantial variation in the characteristics of HCT centers that have different care models to optimize the use of available resources, identifying external benchmarks, and the usefulness of comparative external benchmarks.

The Value of Dashboards for Metrics or KPI

Provide a user-friendly, visual summary of operational and clinical information.

- Utilized to track data, improve operational and clinical performance, promote transparency, and improve accountability.
- Manage a center's performance by using key metrics, quality assurance, process improvement, clinical outcomes, financial growth strategies, and strategic planning outcomes.

KPIs can result in great limitations when used without setting in place operational effectiveness goals; however, goals should drive what you are measuring but measures should not drive goals. The question is: what are HCT centers or programs trying to assess and analyze? Here are some examples for initiative and strategic goals:

- Evaluate resource utilization.
- Reduce volume variability.
- Use existing capacity more effectively.
- Address staff stress and workflow inefficiencies.
- Measure operational function that has an impact on quality.
- Contrast staffing model with other departments or programs.

Dashboard Basics for Quality (Table 9.4)

- Determine key objectives or areas for display.
- Develop key performance indicators/measures for areas related to structure, process, and outcomes selecting best practice benchmarks externally and/or internally.
- Develop your scorecard (Table 9.5), monitor/audit, and over time.
- Use quality management principles to identify areas that require more attention whether exceeding or falling below your set benchmark.

Table 9.4 Sample of scorecard metrics

Indicator	**Benchmark**
Engraftment ANC	≥95% of HCT by day +28
Time to engraftment autologous	100% 10–12 days
Time to ANC engraftment – allogeneic- matched related (MRD)	100% 14–16 days
Time to ANC engraftment – MUD	100% 14–28 days
Treatment-related mortality	**Benchmark**
100-Day mortality – autologous	<5% day
Day 100 allogeneic – MRD	<10% day

- Focus on high-risk high-volume indicators.
- Use quality management principles of process mapping and step analysis to develop an improvement plan or document acceptable outcome.

Challenges HCT Programs Can Embrace

- Developing quality management programs that use a variety of key performance indicators based on regulatory and accreditation requirements and program needs
- Developing internal quality reporting data systems
- Developing international collaboration to identify core measures for transplant programs to capitalize on the opportunity for external benchmarking

Examples of Quality KPI for Clinical SCT Program (Table 9.5)

- Total transplant volumes by type and cell type
- Other cellular therapy – DLI, HPC, volume, and outcomes
- Length of stay by transplant type
- Readmissions within 30 days of discharge
- Bone marrow collections – volume, product cell counts, and recipient outcomes
- Mortality rate at the +30 day, +100 day, and 1 year mark
- Treatment related (non-relapse mortality)

Table 9.5 Sample of template for SCT quality KPI

KPI description (title)	*Percentage of patients with successful engraftment*
Domain	Patient centered
Sub-domain	Clinical outcome
Definition	Percentage of patients with successful engraftment
Calculation	*Numerator*: Number of patients in whom engraftment was successful (success defined as neutrophil count $>0.5*10^9$ *L* for three consecutive days by day plus 28) *Denominator*: Total number of patients transplanted in the first 6 months of the previous 7-month reporting period
Reporting frequency	Quarterly
Unit measure	Percentage
International comparison [6]	*Specialized services quality dashboards – blood and infection metric definitions for 2019/20*
Desired direction	Higher is better
Data source	According to SCT center

- Engraftment by type of HCT and sourced of stem cells, ANC and platelet count, median time to engraftment
- Patient satisfaction (e.g. Press-Ganey-Transplant Survey), case management discharge survey, and donor follow-up reports
- Critical event/quality reviews such as adverse events, intensive care admissions, and data audits
- Transfusion medicine service indicators such as collection, processing, medication administration, infusion, mobilization, and positive microbial reports
- Known complications – GVHD, ECP for GVHD, and infectious disease markers
- Chemotherapy – verification procedure audits
- Donor and recipient screening and informed consent
- Support service reports and focus compliance audits

KPI Administrative Focus Areas

- Staffing
- Patient volume
- Capacity planning
- Strategic planning
- Acuity versus procedure-based metrics
- Length of stay
- Mortality
- Readmissions
- Cost and resource utilization
- Managed care/payer reimbursement
- Analysis by type of transplant
- Analyze by disease type

Conclusion

Performance measurement offers policy-makers in SCT program a major opportunity for improvement and accountability. Securing improved performance measurement often requires active leadership and it should aim to improve the quality of decisions made by all actors within the program. It is important to emphasize that the presentation of performance measurement data and how this influences its interpretation by patients, providers, and the public require more attention, as public reporting has many benefits but can lead to adverse outcomes; mechanisms should be put in place to monitor and counteract these adverse outcomes.

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Chapter 10
Tracking and Traceability

Lex Van der Gouw

Introduction

In the global field of cellular therapy, including stem cell transplantation, traceability of the cellular product is of essential importance to be able to ensure the patient's safety [1]. During the process of donation, transportation, processing and infusion, storage, or disposal, it is critical that the product can be traced from donor to patient and vice versa. Also, in case of any adverse event, such as poor or non-engraftment or infection, traceability is paramount.

Unambiguous identification of a cellular product can only be achieved through unique donation identifiers and uniform, standardized product description. Stem cell products are regularly transported across national borders, thus creating the need for international agreement on product descriptions and unique donation identification.

Another key element in traceability and identification of cellular products is the transfer of product information. To further enhance safety, accuracy and efficiency, increasing numbers of facilities use electronic systems. Transfer of information between such systems also requires international standardisation of electronic donation and product information.

In compliance with the JACIE standards, standardisation and encoding of cellular product descriptions shall be performed according to the ISBT 128 standard terminology or the EuroCode standard.

In this chapter, the basic principles and means to standardisation of product information will be discussed, using the ISBT128 standard as an example. However, these basic principles also apply to the EuroCode standard [2].

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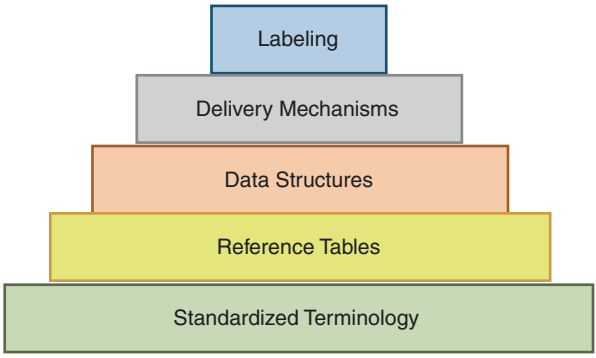


Fig. 10.1 Information environment [1]

Information Environment

Several elements are necessary to create an environment in which information is standardized and transferable between facilities on a global level [1]. Together these elements form the information environment (Fig. 10.1).

The base element is terminology. Without a common international understanding of product descriptions, further attempts to standardisation are useless.

Standardisation in terminology is required to be able to make a distinction between variations in the following product characteristics:

1. Cell type and source, for instance the haematopoietic stem cell, can be derived from blood (apheresis), bone marrow or umbilical cord blood
2. Core attributes, such as storage temperature or the type of anticoagulant used
3. Additional modifications, meaning any manipulation that changes the 'core' state of the product

Product descriptions vary between facilities, nationally as well as internationally. Variations may relate to, for example, storage temperature, the amount of DMSO used in cryopreservation or additional additives after processing. Standardisation in terminology needs a high level of detail to provide the means to make a distinction between different products or track alternations to a product. Once an international consensus in terminology is achieved, this information can be used to generate a product description, based on the three characteristics as mentioned above.

This information should be managed with great care and be accessible to users around the world.

So, with a consensuson terminology, the next layers in the information environment are the reference tables in which this information is stored. With the provided accessibility, facilities around the world are now able to define their products. By combining this standardized information, a unique description of the product is achieved, which can subsequently be uniquely encoded.

Example 1
An autologous apheresis product which is frozen in 10% DMSO solution, with no other additives:

Source:	HPC, apheresis from a mobilized patient
Core conditions:	
Anticoagulant:	Citrate
Storage temperature:	≤ −150 °C
Manipulation:	Adding cryoprotectant 10% DMSO

Together this would generate the unique product description:

- HPC, APHERESIS|Citrate/XX/<=−150C|10% DMSO|Cryopreserved|Mobilized

Example 2
An allogeneic bone marrow product enriched for mononuclear cells (MNC) with added human serum albumin

Source:	HPC, marrow from a non-mobilized donor
Core conditions:	
Anticoagulant:	None, removed during processing
Storage temperature:	Refrigerated
Manipulation:	MNC enriched

Together this would form the unique product description:

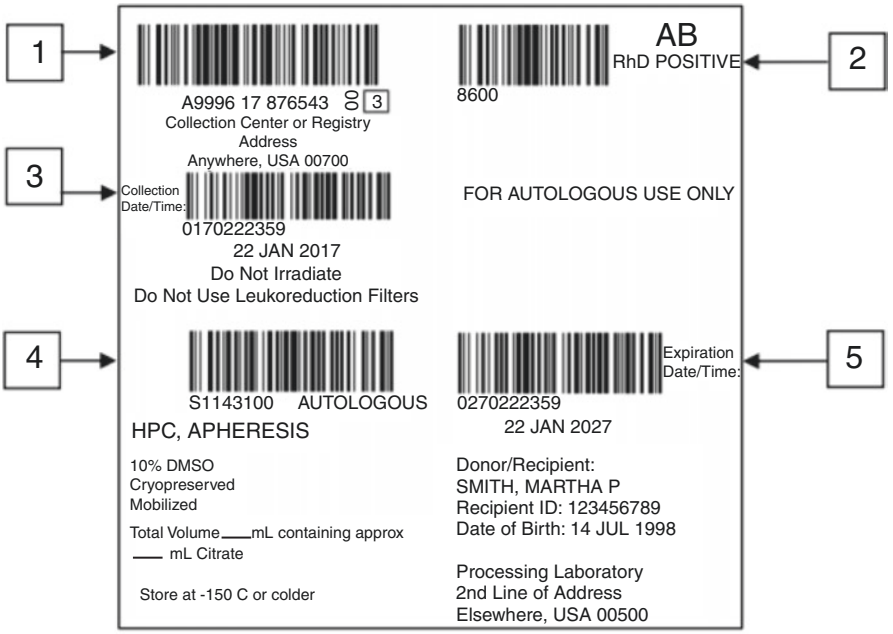
- HPC, MARROW|None/XX/refg|3rd Party Comp: Yes|Mononuclear cell enriched

With the unique product description in place, now one must be able to transfer this information electronically. To achieve this, the product description needs to be converted into a unique, electronically readable, product code and a delivery mechanism is needed, the next two layers in the information environment. Product codes provide the structure and context to be able to decode them to meaningful information. They also provide the link to the reference table so that each product code can be traced to the corresponding product description. Next to the product description, the product code must encode whether or not the product has been divided into separate containers (e.g. a cryopreserved autologous product). Only then, each separate product bag can be traced regarding storage and infusion.

The most commonly used delivery mechanism to transfer information electronically is the linear barcode. As the information that a linear barcode can contain is limited, delivery mechanisms with a higher capacity are also available such as 2D (data matrix) codes. A single data matrix code can hold the same amount of information as several linear barcodes, as shown in Fig. 10.2. The use of a data matrix code is therefore more efficient, especially on smaller labels, and will contribute to a safer and more reliable transfer of electronic information. By using a universal delivery mechanism, such as a barcode, information can now be exchanged between different electronic systems on a global scale.

In the last layer, all previous elements come together to generate a label that contains all the information, eye-readable and electronic, necessary to identify the product and to be able to process that information to maintain traceability. Standardizing the label format and layout such that critical information is placed at

Fig. 10.2 Comparative size of information stored in linear barcode and a data matrix symbol [1]



1 Donation Identification Number
2 ABO/RhD
3 Collection Date/Time
4 Product Code
5 Expiration Date/Time

Fig. 10.3 Standardized ISBT128 label format [3]

fixed positions, as shown in Fig. 10.3, greatly reduces the risk of errors in the interpretation and (electronic) transfer of information.

Donation Identification

Product coding alone, however important, is not sufficient in the unique identification of a cellular product. Without the ability to uniquely trace the donation of a cellular product to the original donor, product coding is meaningless.

Unique identification of a donor is hampered by the sheer number of volunteer donors as well as different donor identification strategies used by international centres [4]. To further enhance safety and reliability in donor identification, the WMDA (World Marrow Donor Association) has developed a global donor identifier (GRID). The GRID comprises identifying information about the facility issuing the GRID and a donor identifier.

Next to unique donor identification, the donation itself also needs a unique, uniform identification.

Similar to the GRID, the donation information contains a donation sequence number and identifying information about the facility that issued the donation number, e.g. a collection facility or registry. In the ISBT 128 coding standard, the year in which the donation took place is also embedded in the donor identification number.

Combining Donation and Product Information

In April 2017, legislation became effective to apply the Single European Code (SEC) on tissue and cell products in compliance with Directive 2004/23/EC of the European Parliament. The purpose of the SEC is that donation and product information are represented in a consistent, combined manner, further aiding the traceability of such products. Basically, the first part of the SEC contains the donation information (facility, sequence number) preceded by a country identifier. The second half contains the product information including a split number and the expiry date. Where the donation identification sequence will not change, the product information sequence changes when the core state of the product is altered.

If necessary, products imported from outside the EU for distribution within the EU will be assigned a donation and product sequence assigned by the importing tissue establishment in order to be able to create an SEC. Records of the original donation and product information and the newly assigned SEC should be maintained in order to link this information for traceability purposes.

In summary, the key elements to the effective, safe, and reliable traceability of cellular products are as follows:

- Unique global donor identification
- Unique donation identification

– Global standardisation of product description
– Data structures to enable digital transfer of information
– Uniform product labelling

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Chapter 11
Adverse Events and Corrective and Preventive Actions

Phuong Huynh and Renza Monteleone

A very important part of the quality programme is the development of a robust system for reporting, investigating, and resolving errors, accidents, adverse events, biological product deviations, and complaints. Reporting and reviewing adverse events (AE) should not be about "blaming" individuals but about assessing if the process which may be at fault can be improved. All personnel should be encouraged to report anything which affects transplant safety [1].

Centres often used a hospital-based incident reporting system, but it may not be adequate to meet the needs of the HSCT programme. Often, not all AEs were reviewed by the programme director and/or a report was issued to the patient's physician. Other significant problems included those related to donor selection and testing, labelling and process control [2]. The HSCT programme should have a system in place which allows the team to follow the management of any occurrences, to propose preventive actions to avoid the occurrences that will happen in the future and to assess the efficacy of those actions.

Prevention of errors is one of the most important aspects of safety in transplantation. Analysis of potential risk factors associated with the entire range of procedures should be part of the overall transplant programme development. Every procedure should be analysed and potential risk factors identified BEFORE they are implemented. Documentation is important to support the investigation of errors, accidents and adverse events, biological product deviations and complaints because these investigations are frequently retrospective [1]. Fundamentally, one should know *where* errors occur in the processes, *why* they occur and *how* to manage them, e.g.

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does quality system include a near-miss reporting system (prevention of errors) and a corrective actions system when incidents have happened?

Definitions of What to Report

- *Adverse Events*/Serious Adverse Events (SAE): any untoward occurrence associated with the procurement, testing, processing, storage, distribution and application of tissues and cells which might lead to transmission of communicable disease, death or life-threatening, disabling or incapacitating conditions for patients or which might result in or prolong hospitalisation or morbidity[1]
- *Near Miss*: an event which, if not identified in time, would have led to an error, accident or adverse reaction or SAE.
- *Biological Product Deviation (BPD)* [3]: any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labelling, or storage, or with the holding for distribution, of a licensed biological product, if that event meets the following criteria:
- Either represents a deviation from current good manufacturing practice (or current good tissue practices), applicable regulations, applicable standards or established specifications that may affect the safety, purity or potency of that product
- Or represents an unexpected or unforeseeable event that may affect the safety, purity or potency of that product:
- Occurs in your facility or another facility under contract with you
- Involves a distributed biological product
- *Complaints*: many institutions have an institution-wide complaints policy in place and the transplant facility will be expected to follow institutional requirements. If there is not a policy in place, then one should be developed and implemented. See Example 5 SOP Adverse.

Investigation, Analysis

While there is no set timeline for investigation, review, and analysis, this should be undertaken quickly so that a potential repeat of the issue is avoided. This aspect should be included in internal specific SOP.

Investigation and analysis in some centres are done through formal review of the entire process to identify where the error has occurred. Collection and processing facilities will have quality incident reporting mechanisms in place and these are shared with the clinical programme where an incident occurred across the linked process, e.g. transportation of the product from collection/processing facility to clinical facility: all parties receive the quality incident report analysis and close the incident. The investigation itself might involve looking at all documentation,

Table 11.1 List of examples templates provided for this section

Number	Title
1.	Types of incident reported
2.	Form to report deviations and near-misses
3.	Registration form for recording complaints, adverse events and near misses
4.	Example of an allogeneic day case inpatient pro forma
5.	SOP adverse event and near-miss reporting

NOTE: This is not a exhaustive list

Example 1 Types of incident reported	
Category	Details
Medication errors	
ABO incompatible blood products	
Malfunction/misuse of equipment	
Contaminated drugs, devices or products provided by facilities	
Labelling of products	
Samples missing or delivered to wrong laboratory	
Results not provided in adequate time	
Signing of drug charts	
Verification of cytotoxic drugs	
Bag damage during thawing of cellular product	
Deviations from policy or procedure if unplanned	
Severe reaction during infusion of cellular product	
Transport issues	
Product found to have positive microbial culture	
Failed engraftment	

training record, having discussions with staff involved and observing the process as it happens.

The forms and reports can be categorised by type, e.g. procedure (e.g. cell reinfusion) and equipment used and then evaluated. This evaluation can be done by specific groups or as part of one of the regular meetings, e.g. quality group. The more frequent events should be prioritised and then resolved (Table 11.1); this can be done by amending policies and procedures, implementing revised worksheets or retraining staff. By doing this, the quality programme is continuously being improved.

Corrective, Preventive Action

Action taken to eliminate the root causes of an existing discrepancy or other undesirable situation to prevent recurrence. As an example, weekly meeting to review with relevant director, quality manager, chief nurse and/or medical

Table 11.2 Example form to report deviations and near-misses; adverse events; occurrences

EXAMPLE TEMPLATE 2 **FORM TO REPORT DEVIATIONS AND NEAR MISSES**
LESSONS FOR IMPROVED CARE SYSTEM Clinical Area: Category: Time: Date: Was there a Deviation from any Policy and/or Standard Operating Procedure : YES/NO What is the Title of the Policy and/or Standard Operating Procedure Deviated from : _____ Job/Role of person completing form: _____
What Happened?
What Immediate Action Was Taken?
What Could Be Changed to Prevent Reoccurrence?
Complete on reverse of form or separate sheet if necessary Was any other type of Incident Form Completed? Reference No.

director and area where incidents occurred. Some centre quality group meetings have errors, accidents and adverse events as part of the standing agenda; group members should include all related facilities. Some centres have separate risk management groups.

The investigation and reporting system is a means of quickly recording near-misses as they occur (Table 11.2). All staff are responsible for completing the forms which ask three simple questions – what happened, what immediate action was taken and what might be done to prevent recurrence of the problem. Each near-miss is categorised, e.g. products, sampling, transport, labelling, infusion, nursing, medical, drugs, pharmacy, result processing. Every day, reports are collected and on a weekly basis, the relevant director, quality manager, head nurse and pharmacy or

other services as required review the documents and discuss corrective actions. Sometimes, thorough investigation is needed and this will involve observations, interviews and complete review of the procedures linked to the near-miss which took place. The results and outcomes are reported back to all departments within the programme and monthly "*Trend*" reports are written to establish whether improvements have been made and are working. Whatever corrective action is taken, e.g. amending an SOP or re-training staff, must be documented, and assessed whether it has achieved the desired impact.

Biological Product Deviations (BPD)

The most common BPDs encountered by clinical programmes involve products with positive microbial cultures or products from ineligible donors. Such products are only used by clinical programmes when evaluation shows that the benefits outweigh the risk to patient if no alternative is available.

In some cases, the relevant information is not known until after the infusion has occurred. Centres are responsible for deciding on whether they will use these products and, if so, under what circumstances. There must be a detailed plan and procedures in place which describe the following:

- Whether a product with positive microbial culture can be used
- In what circumstances its use would be permitted
- How the recipient is protected
- How full record about all aspects of the process is filed

For methods for investigation and review where the BPD was unknown until AFTER the cellular product was infused, centres can also follow the processes above.

Investigation and analysis in some centres are done by reviewing the entire procedure to identify where the contamination might have come from. Collection and processing facilities have quality incident reporting mechanisms in place and these are shared with the clinical programme where an incident occurred across the linked process. All parties receive the quality incident report and meet to analyse and close the incident – the investigation itself might involve looking at all documentation, training records, having discussions with staff involved and observing the process as it happens.

Methods for investigation and review where the BPD was known BEFORE cellular product was infused followed the systems described above. As an example, we present a case whereby a product from an unrelated donor was potentially contaminated due to infection of the donor with a tropical disease. The collection centre advised the transplant centre only on the morning of the collection. In the meantime, at the transplant centre, the recipient was fully conditioned using full intensity conditioning regimens. The reasons behind the potential contamination

were fully investigated and revised processes put into place at the collection facility following close liaison with the clinical facility. The centre had no alternative but to use the product as no other donor was available in time. The centre quickly liaised with specialists at their own centre and external specialists in tropical diseases, and several different samples were sent to different laboratories and results returned within hours prior to cell infusion. All steps were taken to safeguard the recipient (prophylaxis), and the recipient was informed prior to, during and after infusion. Records of the entire process were documented and filed in patient case notes, incident reports, deviations and near-miss reporting with corrective actions clearly shown.

The centre where the BPD occurred BEFORE infusion should investigate the process of collection and infusion with relevant staff and report to medical director of corresponding service, and BPD incidents and reports should be audited regularly. Some centres have separate risk management groups working with all related facilities to develop procedures on how products are managed and reported in accordance with applicable regulations. Policies are in place which cover criteria for release, labelling, notification of recipient, investigation of cause, disposal and timely notification of transplant physician and other related facilities involved. Procedures are in place for dealing with BPD if unknown until infusion has occurred as per JACIE standards [4].

Example 3

Registration form for reporting complaints errors and adverse events		
	Date reported: ……	Quality manager: ……
	Employee ……	Number ……
Informant		
Name:		
Department/address:		
Postcode/place:		
Phone number:		
Nature of complaint or adverse event		
Corrective actions		
Suggestions		
Program director:		
Incident closed: Date:		

Example 4

EXAMPLE TEMPLATE FROM AN ALLOGENEIC INPATIENT DAILY REPORTING PRO-FORMA (PART OF)

SHOWING HOW DEVIATIONS MIGHT BE DOCUMENTED

ALLOGENEIC TRANSPLANT DAILY PRO-FORMA
TO BE COMPLETED IN FULL BY PHYSICIAN ATTENDING AT ALL TIMES OF REVIEW

PATIENT DETAILS

TODAY'S Date :_____ Days Post-Transplant : _____

WEIGHT : _____Kg Performance Status : _____
[Good-ECOG 0-1; Poor - ECOG 2-3]

COMPLETE ON DAY 0 ONLY

Source of Stem Cells : *Bone Marrow / Peripheral Blood / Cord Blood / Other

Ex-Vivo Manipulation : *Yes/No _____ If "Yes": *Negative/Positive Selection

Cells actually infused: $TNC = \frac{\qquad}{\qquad} \times 10^8/Kg\ CD34 = \frac{\qquad}{\qquad} \times 10^6/Kg$

Adverse Events/Reaction to Infusion of Cells: *Yes/No

If "Yes", has an IR1 been completed: *Yes/No

Conditioning Regimen Used

Timetable in Notes YES NO

Was there a Deviation from Planned Timetable YES NO *

If Yes, please give details

_____
_____

WBC x 10^9/L :-	NC x 10^9/L :-	Hb g/dl :-	Platelets x 10^9/L :-
G-CSF	Yes	No	Date Started:
Platelets Needed Today	Yes	No	

Example Template 5

ADVERSE EVENT AND NEAR-MISS REPORTING PROCEDURE HEADINGS
STEM CELL TRANSPLANT PROGRAMME
STANDARD OPERATING PROCEDURE

TITLE: ADVERSE INCIDENT AND NEAR-MISS REPORTING

Code		Issue	No:		No. Of Pages:		Copy No:	

Replaces: Revision :

INDICATIONS FOR PRACTICE
AUTHORISED PERSONNEL/TRAINING REQUIRED (Who is responsible for Reporting and what level of training is required)
PROCEDURE FOLLOWING INCIDENT/NEAR MISS:
What Actions MUST be taken and how is safety assured following an Incident or Near Miss?

WHEN PRINTED
This SOP is for single use only. Please destroy following use.

Effective Date:		Review Date:		Obsolete Date:	
STEM CELL TRANSPLANT PROGRAMME STANDARD OPERATING PROCEDURE					

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Chapter 12
Process Indicators

Olga López-Villar

Introduction, Definitions, and Example

The organization of work by processes is a strategy well established in quality in recent times. It may seem challenging to implement this in the medical field. However, working in a process-based organization will help us establish the quality system since each process has different personnel, different procedures, different risks, controls, indicators, etc. And the interaction between those processes or subprocesses also requires particular detail.

To start with, clarification of some terms is needed because they may look similar [1, 2]:

- Process: A goal-directed, interrelated series of actions, events, or steps.
- Process control: The standardization of processes in order to produce predictable output.
- Processing: All aspects of manipulation, cryopreservation, packing, and labeling of cellular therapy products.
- Product: The easiest way to define it would be "the cells."
- Standard operating procedure (SOP): A document that describes in detail the process or chronological steps taken to accomplish a specific task. It is also referred to as working instructions. An SOP is more specific than a policy.
- Policy: A document that defines the scope of an organization, explains how the goals of the organization will be achieved, and/or services as means by which authority can be delegated.

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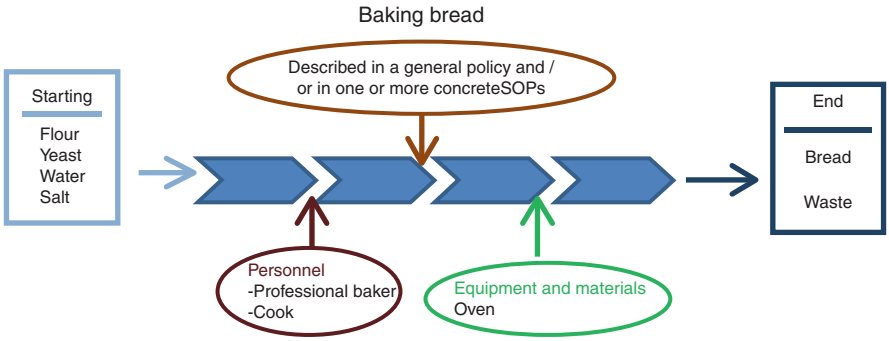

Fig. 12.1 Example of a process

- Quality: Conformance of a product or process with pre-established specifications or standards.
- Quality control: A component of a quality management program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of cellular therapy products, including testing and product release.
- Indicators, also referred to as key indicators or quality indicators: An indicator is a measurement done at a critical point that has to be within a defined range. If not, an action should be taken.
- Example of a process: The process of "baking bread" is simple and quite visual and can serve as an example (Fig. 12.1).

The process has to be validated before opening the bakery (tested to have a certain result), the equipment has to be controlled, there may be a recipet (SOP), etc.

In the process, there shall be controls to assure that the bread is almost the same every time: weight of ingredients, temperature of the oven, etc.

An indicator may be established, depending on the requirements of the clients, the controls of the product, the previous occurrences of the bakery, etc. For example, more than 95% of breads that are sold at a certain price have to weigh ≥500 g [4].

Process Definitions

The transplant process is extremely complicated. It can be treated as a single process with different sub-processes if all the steps are performed in a single institution, or as different processes with a close relationship in case of different entities in the same or in different institutions.

For illustrative purposes, the transplant process has been simplified (Fig. 12.2).

When a transplant program is starting in the quality and accreditation process (it is also a process) they have to work on many aspects, among them the process

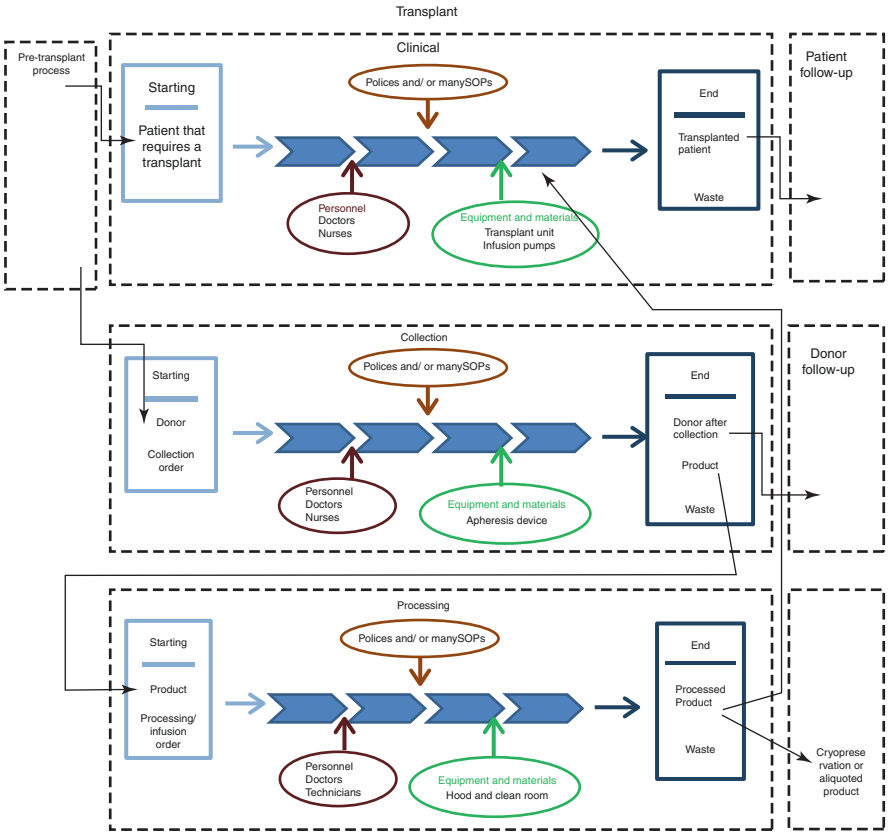

Fig. 12.2 Summary of processes in a transplant program

definitions. They have to be based on the structure of the program, of the organization that hosts the program, responsible staff, etc.

Although it is not mandatory, the division in to at least clinical, collection, and processing processes can be a start. Those procedures shall have a clear interaction, whether being performed in the same or different institutions.

In the annual review, the indicators of the processes and other issues are included. A change to the processes may also be required within time and has to be carefully analyzed (risk assessment), planned, and implemented, to be further analyzed again.

Process Controls

The process controls are described in detail in the current edition of FACT-JACIE standards [1, 2].

CM8 – Marrow collection process controls include procedures, inventory, equipment, blood components, written order for collection, peripheral blood count to proceed, suitability prior to collection, anesthesia, mobilization, quality of the product, aseptic technique, pediatric donors, packing, filtration, and records.

C8 – Apheresis collection process controls include the ones seen for marrow collection (except for the different requirements for the filtration of bone marrow), plus some specific controls regarding central lines.

D8 – Processing process controls include manufacture of the product, written request, specific information for allogeneic donors, validated processing procedures, identification of critical control points, aseptic technique, microbial contamination, records, review of processing record, end points not met, more-than-minimal manipulation, blood group and antibody screen, cord blood, and sample storage.

Clinical program controls: Through all the chapter of clinical standards, a number of controls are indicated: control of airborne microbial contamination, document control, and outcome analysis (see Chap. 6). In fact, among the principal controls for the clinical unit are the ones described in the outcome analysis chapter and also performance measurements (see Chap. 9) and benchmarking.

A unit can require further controls, depending on the different procedures performed.

Process Indicators

Selection, Definition, and Range

How to choose an indicator?

As indicated in the definitions, an indicator is a measurement done in a critical point that has to be within a defined range. If not, an action should be taken. They are used to monitor the quality of the process [3, 4].

In a visual way, it is like a thermometer. If the measured value is above or below a certain level, there are no major issues, and one can continue working the same way. But if for instance the value is above that level, it is like having fever, which means that there is a problem that has to be studied and treated.

Indicators can be different among transplant programs. They have to be selected based on the risky points of the process and procedures, on the occurrences detected in the previous months or years, etc.

It is important to remember that if the indicator is not within the range, an action should be taken. For example, it is difficult to define the "number of transplants per year" as an indicator. It is a measure of the activity. An indicator requires an objective level. If you select as quality indicator "more than 100 transplants per year," you have to think if there is any action to be performed if a year there are 90 transplants (probably not).

A way of starting would be taking into account the process controls that have been briefly reviewed before. Transplant programs do have data on those

parameters, some of them with associated occurrences or that have been shown in audits or in the risk assessment to be "difficult" or "critical."

The parameters included in the outcome analysis are often used as indicators, for example, neutrophil above 500/μL at day X in ≥90% of transplants and/or graft failure in ≤5%. The accepted level or the accepted range has to be defined according to the center experience, the literature, etc. An individual delay in engraftment in a certain patient may be studied as an occurrence and a graft failure as an adverse event. But those are the studies on individual patients. But if those cases become more and more frequent in the transplant program, a detailed review of the system and a corrective action should be implemented. In these cases, the study should include not only clinical aspects (data of the patient, lines of chemotherapy, time to recover, conditioning, etc.) but also aspects of collection and processing, for example, number of cells and potential issues affecting viability. After reviewing the potential causes, an action should be taken and analyzed at a later step.

Regarding indicators of collection, a typical example would be collections finished with the number of cells ≥X% or efficiency of collection above a certain level in a percentage of procedures. Regarding the procedure itself, depending on the program, other useful indicators would be percentage of side effects, etc.

In processing, the indicators are focused on the product: products with positive culture below a certain percentage, viability over a certain percentage, etc.

The definition of the indicator has to be clear: what are we going to measure and how [5]? The definition, the range, etc., have to be included in quality documents. The way to obtain details to do the measure can be by reviewing the patient's clinical data or the collection or processing procedures, etc.

Persons Responsible for the Measure and Timing

Depending on the indicator and on the organization, indicators can be measured by a person directly related to the process (e.g., nurse of collection) or indirectly by the quality manager.

How often are indicators measured?

It depends on the point to measure and the urgency to take measures if the indicator deviates. They can be monitored monthly, quarterly, or, in some particular indicators, on a yearly basis.

Indicator's Table

After defining what and how to measure, by whom, and when, it can be useful to have a summary in a table (Table 12.1). This table would be filled with the results and the actions taken. And in a quick view, you can see the evolution of the measure within time.

Table 12.1 Example of indicator's table

Indicators							
Clinical indicators							
	Title	Objective	1st T	2°T	3°T	4°T	Year
1	Graft failure	≤Stablished %					
2	CVC infections	≤Stablished %					
	Others						
Collection indicators							
	Title	Objective	1st T	2°T	3°T	4°T	Year
1	Side effects	≤Stablished %					
	Others						
Processing indicators							
	Title	Objective	1°T°	2°T	3°T	4°T°	Year
1	Microbial contaminations	≤Stablished %					
	Others						
Actions taken							
	Indicator deviated	Period	Action taken				

T **trimester**

The table may be split in clinical, collection, and processing if those units are independent. But results have to be shared with the entire program.

Actions

If the indicator falls above or below the target level, a corrective action shall be done. If an indicator is about to reach the level, a preventive action should be carried out in order to avoid reaching the dangerous level. For the development of corrective and preventive actions, see Chap. 11.

The action can be registered in the indicators panel (Table 12.1) or in the forms for occurrences. The deviation in the indicator, study of the cause, actions, etc., have to be opened and reviewed as other occurrences of the unit. The effectiveness of the actions has to be reviewed and will be seen in the following measures of the indicator.

Other Indicators

Besides the indicators seen, other key indicators may be required to monitor other aspects of the program. Indicators of the quality system itself may be required in other systems to review and keep under control particular points (e.g., corrective actions reviewed on time).

When selecting the process indicators, take into account that they have to be useful. It is not about having a long list, or indicators difficult to measure, but they have to be a practical tool to measure and improve the quality system.

Indicators Within Time

Indicators are a dynamic tool. If one gets better and better results in the point of measurement, a more demanding objective can be set.

If occurrences start to happen in a certain part of the system, or if a new issue appears on the risk assessment, a new indicator can be opened to measure it more frequently and keep it under control.

In the same way, if a previously not-controlled issue gets to be fully compliant in each patient, year after year, having an indicator may not be as useful as before. It could be considered to be closed. If occurrences in that issue are seen again, it can be started again.

Communication

The measure of the indicators is a fundamental part of the quality management system. They have to be shared in the regular quality meetings.

They have to be included also in the annual review of the system [2]. To assess if an improvement is seen, a comparison with the indicators of the previous years is also advisable.

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Chapter 13
Writing a Quality Management Plan

Mara Magri

Introduction

Quality management systems (QMS) are central to FACT-JACIE accreditation standards [1]. As the first edition of the JACIE standards has been published, every haematopoietic cell transplant (HCT) programme must decide on how to develop and implement its QM programme via a written quality management plan (QMP). The QMP should be "just right" for the type and size of an HCT programme. It should be a top-level overview of how the organization operates, aimed at implementing quality improvement whilst being realistic and deliverable. The QM plan (QMP) is usually collected in a single document, often and interchangeably referred to as the 'quality manual', that outlines how the QMS is implemented and managed.

Although JACIE standards require that the HCT programme has a QMP/quality manual, the style and structure are not specified. There is considerable flexibility in how to prepare it, and an HCT programme can construct the QMP so that it is most useful and suited to the needs of the organization and ultimately patient care.

When writing a QMP, it is good practice to create a working group. The QMP needs to be tailored to the specific needs of the HCT programme, so each facility should carefully consider how to best involve those who are needed. Also, the development of a comprehensive QMS is often the most challenging and time-consuming exercise that a clinical programme encounters when preparing for JACIE accreditation.

As HCT programs are almost always part of a broader healthcare organization, they can apply policies and procedures of the existing institutional QMS, for example, ISO certified, or they can have a standalone QMS. An integrated HCT programme may, but is not required to, have one QMP that addresses all aspects of the

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clinical, collection, and processing facilities. If managed across organizational boundaries, there must be clear evidence of relationships among the QM programmes, usually associated with service-level agreements (SLA) detailing roles and responsibilities.

A generic, too broad, or poorly written QMP may be an indication that the QMS is not deemed an integral and important component of the HCT programme.

The key points to remember about the QMP are as follows:

- There is only one official version.
- It should be a *working document*. It is never finished – it is always being improved.
- It should be *read, understood,* and *accepted* by everyone.
- It should be written in *clear*, easily understood language.
- It should be dated and signed by the *leadership* (HCT programme director or designee).
- It should describe the system as it is operated and *not a description of an ideal world.*

QMP Structure

The QM plan must detail all key elements that affect the quality of recipient and donor care and cellular therapy products as described in the FACT-JACIE standards and manual. The specific SOPs to be followed for each of these elements does not have to be fully repeated in the QMP, but must be briefly summarized and referenced within the QMP and linked to the appropriate document where the details are described. Quality is the responsibility of all personnel involved in the HCT programme.

Although there is considerable flexibility in how to prepare a QMP, the content and structure should address the elements listed below.

– Organization – roles and responsibilities
– Personnel – qualification, training, and competency
– Document control
– Outsourced activities management (contractual arrangements)
– Quality control – key performance data and outcome analysis
– Self-assessment and internal and external audit
– Investigation and reporting of deviations, adverse events, reactions, and complaints
– Traceability
– Disaster and contingency planning
– Qualification and validation
– Quality risk management
– Tools for continuous quality improvement
– Operational environment

– Premises and infrastructures
– Equipment and materials supply

If there are no organizational boundaries, it could follow the index of FACT-JACIE standards and manual, to be sure of having addressed all requested quality elements.

PLEASE NOTE: The basis for all audits and assessments of the QMS, including JACIE inspection, will be based on the contents of the QMP and the documents to which it refers.

HCT Programme Description

The QMP should begin with an introduction that contains an overview or description of HCT programme, its history, where it is located, how many beds/staff, basin of reference, type of procedures performed, i.e. autologous and/or allogeneic transplantation, paediatric and/or adult setting, clinical unit only, collection only, etc. It gives basic but important information about the HCT programme organization, interaction and activities; it is helpful for users and new staff and shows how changes occur over time. In case of an integrated HCT programme, the collection/processing profile would also be documented under this heading even if they have their own QMP.

Organizational Structure – Roles and Responsibilities

The QMP shall include or summarize and reference an *organizational chart of key positions and functions* within the HCT Programme, including clinical, collection and processing with a clear description of how key positions interact to implement the QMS in the HCT programme [2].

The overall organizational chart should include the titles of key positions and the reporting structure of the HCT programme. The chart should also outline the relationship among the different sections of the HCT programme (clinical, collection and processing at a minimum) even if supporting functions are performed by contract with other facilities or organizations. Lines of responsibility must be clearly defined in a way that is understood by all involved. It would be useful, but not mandatory, outlining the names of the key positions and verifying its applicability and correctness (Fig. 13.1).

Keeping clear and active communication within the HCT programme and between the HCT programme and any other departments and health care professionals is fundamental for the quality of processes performed.

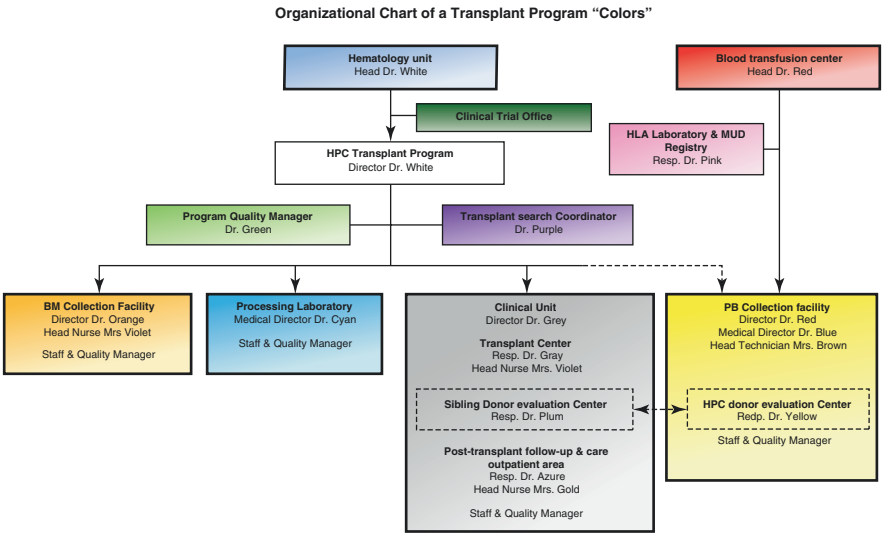

Fig. 13.1 The organizational chart of the "Colours" HCT programme

For example, JACIE standards require guidelines for communication with both the collection facility and the registry in the event of collection-related complications. Moreover, if responsibilities in donor selection, evaluation and management are shared, documented communication between teams is required.

It is clear then the HCT programme should address all these aspects in the QMP or in any other policy or procedure, detailing the methods of communication used such meetings, mails, reports and oral communication. The HCT programme should also describe when using one method instead of another. (i.e. written report for sharing of quality data among key individuals within participating facilities in the HCT programme).

Key Personnel – Qualifications, Training, and Competency

The QMP should address policies and procedures (normally kept separate from the quality manual itself) summarizing personnel requirements for each key position in the HCT programme.

These should include at least: a job description, initial qualifications, new employee orientation, initial training, competency, and retraining when appropriate, continued competency assessed annually and continuing education.

All persons working in the HCT programme must have an accurate and clearly defined job description. Documentation of training for everyone must include all procedural skills routinely practiced. These requirements are detailed in FACT-JACIE standards and manual.

Document Control

The QMP shall include or summarize and reference a system for *document control* with the identification of the types of documents that are considered critical for the HCT programme and with the description of how they are controlled (Fig. 13.2). A critical document refers to a document that is directly related to and could impact patient care or cellular therapy product integrity.

The hierarchy and number of documents or extent of documentation is dependent on the processes, the size and the complexity of the HCT programme and will differ from one organization to another.

There are many different types of documents such as policies, SOPs, operative instructions, guidelines, protocols, providing description of activities and processes performed by the HCT programme. Other types of documents such as worksheets, checklists, records or forms are essential tools to provide quality control and evidence of conformity to FACT-JACIE standards (provision of evidence that what was planned has actually been done).

If the HCT programme participates in an existing QM programme in its Institution, it can or has to use portions of the hospital's QM programme, in

Document type	Document Code	Responsibilities				Distribution from to	
		Writing	Review	Approval	Archive		
Quality Manual	QM Programme or QM ± Facility	Staff	Director (HCT Programme)	Director (HCT Programme)	Quality Manager	Quality Manager	Staff
			Quality Manager	Executive board			stakeholders
Quality Plan	QP ± Facility ± Area + XX	Quality Manager	Quality Manager	Director (HCT Programme)	Quality Manager	Quality Manager	Staff
							Executive board
Procedure	SOP ± Facility ± Area + XX	Staff	Quality Manager	Director (HCT Programme)	Quality Manager	Quality Manager	Staff
Guideline	GL ± Facility XX	Responsible of the activity or service	Quality Manager	Director (HCT Programme)	Quality Manager	Quality Manager	Staff
			Director (HCT Programme)				
Protocol	Prot ± Facility ± Area + XX	Staff	Quality Manager	Director (HCT Programme)	Quality Manager	Quality Manager	Staff
Instruction	I ± Facility ± Area + XX						
Annex	A + Document code + XX						
Table	Tbl + Document code + XX						
Flyer, Leaflet, booklet	Inf ± Facility ± Area + XX	Staff	Director (HCT Programme)	Director (HCT Programme)	Quality Manager	Staff	stakeholders
				Executive board			
Checklist / Form / worksheet	C/L / F/Ws + Document code + XX	Staff	Quality Manager	Director (HCT Programme)	Facility / Program me staff	Quality Manager	Staff
Agreement	Registration XX	Responsible of Parties involved	Director (HCT Programme)	Director (HCT Programme)	Director (Facility / Program me)	Executive board of Parties	Staff
				Executive board of Parties			Parties involved
Laws & Regulation		/	/	/	Quality Manager	Quality Manager	Staff

Fig. 13.2 Document control table of the "Colours" HCT Programme

particular for the document control system. In this case, the quality manual can summarize and reference institutional policies or procedures for document control with due regard to any differences with FACT-JACIE standards (i.e. storage period of obsolete documents).

The system for document control should describe policies for the following:

- Document development and implementation, using a standardized format for critical documents, and assign a numeric or alphanumeric identifier, a title and a version.
- Document approval, including the approval date, signature of approving individual(s), the effective date and distribution.
- Document review and revision or change control that includes a description of the change, version number, the signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date and archival date.
- Document protection from accidental or unauthorized modification.
- Document archival, the inclusive dates of use, and their historical sequence for a minimum of 10 years from archival or according to governmental or institutional policy, whichever is longer.
- Retract obsolete documents to prevent unintended use.
- Establish and maintain *written agreements* with external parties providing critical services that could affect the quality and safety of the cellular therapy product or health and safety of the donor or recipient.

The quality manual can summarize and reference institutional policies and procedures also for *agreements* preparation, outlining the roles and responsibilities of each party for the performance of critical tasks to maintain accreditations and to comply with applicable laws and JACIE standards. Agreements shall be dated, reviewed, revised on a regular basis as defined by the HCT programme, and at least every 2 years, and approved by both parties and by legal representative of the parties.

The term *agreements* includes the *contingency plans* with an external facility such as service-level agreements, contracts and preventive maintenance arrangements, and written agreements with donor registries and external laboratories performing testing of donors, recipients or cellular therapy products.

Moreover, the QMS shall ensure that essential services for patients are not interrupted. Each facility of the HCT programme – from collection to processing and administration of cellular therapy products – should have a continuity plan in place that details how services will be maintained if activities must temporarily be suspended or permanently ceased. Usually this plan will include a mutual agreement (a service-level agreement or contract) with another organization for the transfer of product, documentation and services in these circumstances.

For the emergency and disaster plan, the HCT programme may use institutional policies for the general responses; however, specific SOPs and agreements with external facilities to address the safety of recipients and donors and of stored cellular therapy products are needed to augment the institutional policies.

An HCT programme within a single institution is not required to have written agreements for the collection and processing facilities.

Key Performance Data and Outcome Analysis

The quality manual shall include or summarize and reference policies and procedures for the collection and analysis of the selected *key performance indicators* (from clinical, collection, and processing facilities) and their review by the Program Director at least once a year. *The outcome analysis of clinical data and the other quality measures, described in the paragraph "Tools for continuous quality improvement", are usually part of the annual report and they provide clues on areas for improvement and documented evidence of* the effectiveness of the QM Program (Fig. 13.3). All monitoring, measuring and evaluation outputs shall be documented, analysed and reported to staff and the HCT programme will choose how to aggregate data based upon its size and complexity.

The parameters to be monitored or reviewed in a regular fashion should be identified in the quality manual and they should address all key elements of the HCT programme such as the safety and efficacy of the cellular therapy product, and the clinical outcome and adverse events related to the recipient, donor or product. These data shall be provided in a timely manner to facilities involved in HCT programme activities.

The HCT programme is also encouraged to define internal benchmarks and compare them to national or international data.

<table>
<tr><th>Clinical Unit indicators</th><th>Transplant activity indicators</th><th>Collection facility</th><th>Processing Facility</th></tr>
<tr><td>N° of inpatients/year</td><td>N° of transplants /year (allogeneic and/or autologous)</td><td>N° of potential donors evaluated / year</td><td>N° of cryopreserved procedures / year</td></tr>
<tr><td>Mean length of stay</td><td>N° of follow up examination for allotransplanted patients/year</td><td>Time from donor starting evaluation to final selection</td><td>N° of cryopreserved bags / year</td></tr>
<tr><td>Index of bed occupation</td><td>Time from donor search activation to final selection of an HSC donor</td><td>N° of donors collected / year</td><td>N° of clonogenic assays / year</td></tr>
<tr><td>Index of turnover</td><td>Time from donor search activation to transplant</td><td>N° of collection per patient</td><td>% of viability after thawing (mean)</td></tr>
<tr><td>Index of bed rotation</td><td>N° of withdrawn donor workups / N° of activated donor workup per year</td><td>cell yield per collection</td><td>CD34+ cell recovery (post processing vs post thawing)</td></tr>
<tr><td>N° of new diagnoses/year</td><td>Waiting list for transplant</td><td>duration of each collection</td><td>N° of validation procedures / year</td></tr>
<tr><td>N° of follow-up visits/year</td><td colspan="3">Engraftment (time to recovery of neutrophils > 0.5 x 10^8/L and platelets > 20 x 10^8/L)</td></tr>
<tr><td>N° of falls/year</td><td>N° of no engraftment/year</td><td></td><td></td></tr>
<tr><td>Clinical trials indicators</td><td>overall and treatment-related morbidity and mortality (at 30 -100 days and 1 year after transplantation</td><td colspan="2">% of products with positive microbial culture results</td></tr>
<tr><td>N° of Phase I clinical trials with active enrolment</td><td>aGvHD grade within 100 days and cGvHD grade within 1 year after allogeneic transplantation</td><td colspan="2">N° of non-compliant products / year</td></tr>
<tr><td colspan="4">N° of internal audits/year</td></tr>
<tr><td colspan="4">N° of Nonconformities (product, process, service)/year</td></tr>
<tr><td colspan="4">N° of adverse events (product infusion, chemotherapy treatments) / year</td></tr>
<tr><td colspan="4">N° of complaints / year</td></tr>
<tr><td colspan="4">N° of staff training and education activity</td></tr>
<tr><td colspan="4">N° of peer review publications</td></tr>
<tr><td colspan="4">N° of SOPs reviewed / N° of SOPs to be reviewed</td></tr>
</table>

Fig. 13.3 Key performance data of HCT Programme "Colours"

Even the frequency for data collection and analysis should be established in the QMP. Some indicators may be reported with each occurrence, while others may be prospectively analysed and reported at defined intervals (i.e. during the QM meeting or the annual HCT programme review) to determine causes of issues and make improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement.

FACT-JACIE standards state which data for each type of cellular therapy product and recipient type shall be evaluated. Some of them are as follows:

- Time to engraftment following cellular therapy product administration (HPC products)
- An endpoint of clinical function for immune effector cells
- Overall and treatment-related morbidity and mortality at 30 days, 100 days and 1 year after cellular therapy product administration
- Acute GVHD grade within 100 days after allogeneic transplantation
- Chronic GVHD grade within 1 year after allogeneic transplantation

Audits

The QMP shall include or summarize and reference policies and procedures for planning and conducting *audits* of the HCT programme's activities to verify compliance with QM documents, applicable laws, or regulations, and JACIE standards.

If the HCT programme participates in an existing QMS in its institution, it can or has to use institutional policies or procedures for audit process. In this case, the quality manual can simply summarize the audit process and reference institutional procedures with due regard to any differences with JACIE standards (see "the compulsory audits" in FACT-JACIE standards and manual).

Alternatively, the audit process can be detailed in the QMP or in a dedicated procedure of the HCT programme describing the following:

- Different kinds of audit available for different purposes (self-assessment, internal and/or external audits)
- Competences and the expertise of auditors
- Audit annual planning
- Preparation of an audit programme
- Management of the results of audits

The Management of Products with Positive Microbial Culture Results

The QMP shall include or summarize and reference policies and procedures for the management of cellular therapy products with positive microbial culture results.

This quality element can be merged with the next one paragraph addressing problems and errors management or it can be treated in a dedicated procedure. In all cases, the QMP shall describe at a minimum the following aspects:

- Criteria for the administration of cellular therapy products with positive microbial culture results
- Notification of the recipient (who, how, informed documentation)
- Recipient follow-up and outcome analysis
- Follow-up of the donor if relevant
- Investigation of cause (as described in the next paragraph)
- Reporting to regulatory agencies if appropriate

For each aspect, the HCT programme should detail what action is to be taken, who is responsible to take the action and the expected timeframe of the actions.

An over-arching document for the management of cellular therapy products with positive cultures is recommended because it could involve the clinical unit, the processing and/or the collection facility.

The Management of Occurrences

The QMP shall include or summarize and reference policies and procedures for *occurrences.* This term (which could be understood as non-conformity) refers to errors, accidents, deviations, adverse events, adverse reactions and complaints. As described in paragraph "Audits", if the HCT programme participates in an existing QM programme in its institution, it can or has to use institutional policies or procedures for the management of occurrences. In this case, the quality manual can simply summarize the process and reference institutional procedures with due regard to any differences with FACT-JACIE standards. Nevertheless, the HCT programme should define errors, accidents, deviations, adverse events, adverse reactions and complaints and describe when, how, by whom and to whom each is reported. The HCT programme should define when events need CAPA plans along with their plan to audit the effectiveness of the changes.

Alternatively, the management of occurrences can be detailed in the quality manual or in a dedicated procedure of the programme describing the following activities:

- Detection
- Investigation
- Documentation
- Reporting
- Corrective and preventive action

Traceability

Traceability describes the ability to verify the origin, location, or application of an item by means of documented recorded identification.

In JACIE standards, *traceability* means the ability to locate and identify the cellular therapy product, the donor and the recipient during any step from procurement, through processing, testing and storage, to distribution for transplant to the recipient

GUIDE TO THE QUALITY AND SAFETY OF TISSUES AND CELLS FOR HUMAN APPLICATION

	Donor centre	National registry	WMDA	Collection centre	Tissue establishment	Transplant centre patient
Activities	Consent Testing Donor follow-up	Listing Donor and patient follow-up	Listing	HPC collection	Product labelling, processing and release	Infusion Patient follow-up
Donor data*	ID code Identity	ID code Identity of National Registry donors only	ID code only	ID code Identity	ID code Product code (e.g., SEC)	ID code only
Patient data*	ID code Identity	ID code Identity	NA	ID code Identity	ID code Identity	ID code Identity

WMDA: World Marrow Donor Association.

The identity and privacy of all patients and donors are protected throughout the process of HPC donation and transplantation (Identity=name).

* Anonymous contact between patient and donor allowed post-transplantation only through Registry.

Fig. 13.4 Traceability of unrelated haematopoietic progenitor cells donor and recipient data

or disposal. Traceability also applies to the facilities and personnel involved in the above mentioned activities so it implies the ability to identify the collection facility, the tissue establishment and the Clinical Unit in each step of the process (Fig. 13.4). [3].

Given the premises, the quality manual shall include or summarize and reference policies and procedures for cellular therapy product tracking and tracing that allow full traceability of donations from donor to recipient, all materials, reagents and equipment that come into contact with cellular therapy products and tracing from the recipient or final disposition to the donor.

A policy for the traceability of all patients and their clinical and medications data (including blood transfusions) is also mandatory to guarantee patient safety.

If the HCT programme participates in an existing QMS in its institution, it can or has to use institutional policies or procedures for traceability (i.e. medical records management, inventory management, drug prescription and administration). In this case, the quality manual can simply summarize the process and reference institutional procedures with due regard to any differences with FACT-JACIE standards.

Business Continuity Policy

The HCT programme should be prepared for situations that may interrupt operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or procedure is required that addresses emergencies and disasters as describe before (see paragraph "Document control"), the HCT programme must also have a plan for the management of temporary interruptions (actions to take, who needs to be contacted, how to prioritize cases, key personnel to be involved and notification of staff).

The QMP shall include or summarize and reference policies and procedures for actions to take in the event the *HCT programme's operations are interrupted*.

For computerized systems of critical processes (e.g. electronic health record, computerized drug prescription), provision (e.g. business contingency plan) should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system).

Generally, the institutional information technology department ensures that softwares in use are validated for their function and that there is a regular schedule of back-up to allow for retrieval of information when necessary. In this case the quality manual can simply summarize the process and reference institutional procedures with due regard to any differences with FACT-JACIE standards.

Qualification and Validation

General Principles

Validation is the part of the QMP concerned with proving that all critical aspects of the HCT programme operations are sufficiently under control to provide continual assurance that product/service will remain safe for patients and fit for purpose.

Validation is usually split into two components: qualification and process or test-method validation.

The term *qualification* is applied to each part of the process including facilities, equipment, computer systems, materials and operators. Each item should be qualified separately to demonstrate consistent performance. Process validation should only be performed once all the items used have been qualified.

The quality manual shall include or summarize and reference policies and procedures for *qualification* and for *validation or verification* of critical procedures.

Sometimes a procedure regarding qualification and validation called validation master plan (VMP) could be in place for the processing facility. In this case, the QMP can simply summarize the processes and reference this VMP, applying it even to bone marrow and peripheral blood collection facilities.

Alternatively, the qualification and validation process can be detailed in the QMP or in a dedicated procedure of the HCT describing the following:

- Key elements of the process to be qualified (i.e. critical manufacturers, vendors, equipment, supplies, facilities, operators and services)
- Critical procedures to be validated
- Preparation steps of the qualification plan
- Preparation steps of a validation plan
- Management of the results
- Approval of the qualification and validation plans, results and reports by the quality manager and HCT programme director or designee

Quality Risk Management

Evaluation of risk is a process to assess and document the risks involved in a change in a process, procedure or environment that has the potential to affect a critical procedure (patient care safety, product integrity, sterility, viability and/or recovery).

The QMP shall include or summarize and reference policies and procedures for the *evaluation of risk* before introducing a new activity and changes to a process to confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation. Risk assessment is not a once-only process but a cyclical one (Fig. 13.5) considering a continuous re-evaluation of residual risk.

Since the risk assessment represents a basic step to go through in the validation process and it is one of the key elements also for ISO standards, the HCT programme could have a dedicated procedure for it. In this case, the quality manual can simply summarize the processes and reference to the existing document.

Alternatively, the risk assessment process can be detailed in the QMP or in a dedicated procedure of the HCT programme describing the following elements:

- Approach to risk assessment used (i.e. brainstorming, Hazard Analysis and Critical Control Points (HACCP), Failure Mode and Effects Analysis (FMEA) and Failure Mode, Effects and Criticality Analysis (FMECA)).

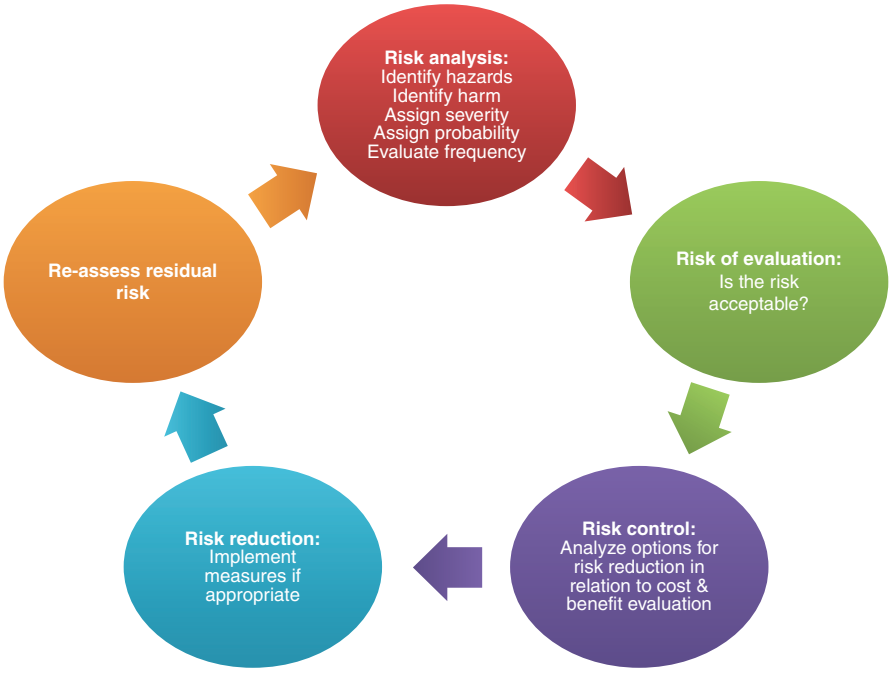

Fig. 13.5 Cycle of risk assessment of HCT programme "Colours"

- Policy regarding risk acceptance
- Mitigation planning (target, task, responsible person, deadlines)
- Evaluation of residual risk (monitoring and re-assessment)

Obtaining Feedback

The quality manual shall include or summarize and reference policies and procedures for *obtaining feedback* from associated collection and processing facilities and from donors and recipients or legally authorized representatives. It may be obtained directly by the HCT programme; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys.

Tools for Continuous Quality Improvement

Products, services or processes of the HCT programme should be constantly evaluated and improved for efficiencies, effectiveness and compliance (Fig. 13.6). If the HCT programme participates in an existing QMS in its institution, it can or has to use institutional policies or procedures for continuous quality improvement system. In this case, the QMP can simply summarize the process and reference institutional procedures with due regard to any differences with JACIE standards. Alternatively, the continuous quality improvement system can be detailed in the QMP or in a dedicated procedure of the HCT programme describing the structured planning approach to evaluate the current practice processes and improve systems and processes to achieve the desired outcome.

Input to management reviews shall include at a minimum the following:

– Key performance data and outcome analysis
– Quality objectives (i.e. document control management with SOPs introduced or revised)
– Quarterly reports of the quality management activities

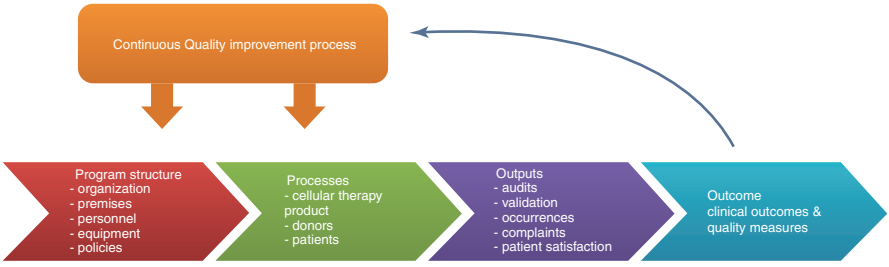

Fig. 13.6 Continuous quality improvement process of the "Colours" HCT programme

– Qualification and validation results
– Non-conformity and CAPA
– Customer complaints and feedback
– Inputs from employees, suppliers and other interested parties
– Results of internal and external audits
– Personnel education and training reports (continuing medical education, competence evaluation)
– Assessment of the adequacy of the resources available (personnel, premises, equipment)

As described in the paragraph "Key performance data & outcome analysis", the QMP should describe the frequency for data collection and analysis. The representative in key positions involved in the quality management review should be defined, as well as the means of communication to the HCT programme staff of Key performance data and review findings (at a minimum on an annual basis), and the type of documented information to be retained (i.e. the minutes and attendance lists).

Other Aspects

The QMP can also provide information on other key elements of the quality management system of the HCT programme such as the following:

- Operational environment
- Premises and infrastructures
- Equipment and materials supply

If the HCT programme participates in an existing QMP in its institution, it can or may even have to use institutional policies or procedures. In this case, the QMP can simply summarize the abovementioned elements and reference institutional procedures with due regard to any differences with FACT-JACIE standards. Alternatively, some aspects like operational environment equipment and supply management can be detailed in the QMP or in dedicated procedures of the HCT programme.

Typically, the QMP of the processing facility might include a map of the laboratory premises, showing all space that the laboratory uses and restricted points of access. The reagent section might address order procedures, storage requirements, preparation and quality control of reagents.

Also, requirements for instrument/equipment management should be addressed in the QMP or in dedicated procedures of the HCT programme, including the following:

- Instrument logbooks management
- Written procedures for use and preventive maintenance
- Procedures for instrument replacement and disposal

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Chapter 14
The Accreditation Process

Mara Magri and Raquel Espada Martín

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 [3]. 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 [2]. Ever since, HCT has continued to be a pioneer in setting agreed clinical quality standards [5, 8] and subsequent external inspection and certification via the process of accreditation (via JACIE). An accredited programme can therefore demonstrate that it is performing at a required level of practice in accordance with agreed standards of excellence, including operating an effective quality management system (QMS). Such a hallmark of quality provides reassurance to healthcare professionals, health service payers and, most importantly, patients and their families.

The accreditation process is divided into three phases. The first phase is a pre-inspection phase where the applicant submits the relevant documentation 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 pre-inspection 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 findings and observations in the inspection report which is reviewed by the accreditation committee which decides on the next steps

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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 identified 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. After achieving the accreditation, the main challenge for the programme is to maintain all the aspects, including the QMS, making it more robust and adhering to the new editions of the FACT-JACIE standards and manual.

Why Seek Accreditation?

Accreditation is the means by which a centre can demonstrate that it is performing a required level of practice in accordance with agreed standards of excellence and certify that it operates an effective QMS.

A quality management system is a mechanism to ensure that procedures are being carried out in line with agreed standards with full participation by all staff members. In an HCT programme, this ensures that the clinical, collection and laboratory units are all working together to archive excellent communication, effective common work practices and reassurance for patients. It is a means of rapidly identifying errors or accidents and resolving them so that the possibility of repetition of the problem is minimized. It assists in training and clearly identifies the roles and the responsibilities of all the staff.

Once the required level of quality has been achieved through modifications to practice, the remaining challenge is to maintain this standard of practice. With a working quality management system in place and adequate resources, the fundamental elements necessary to sustain the programme are continued staff commitment and vigilance.

Initial evidence of a positive relationship between the implementation of a QMS and an outcome of HCT in Europe was published in 2011 [6]. In this paper, patients' outcomes were systematically better when the HCT centre was at a more advanced phase of JACIE accreditation and independent of year of transplantation and other risk factors. Another analysis [7] was performed on a large cohort of patients who received either an allogeneic or an autologous HCT between 1996 and 2006 and reported to the EBMT database. The authors showed that the decrease of overall mortality in allogeneic HCT procedures over the 14-year observation period was significantly faster in JACIE-accredited centres, thus resulting in a higher relapse-free survival and overall survival at 72 months from transplant. Such improvement was not shown in autologous transplantation. Similar results published in an American study [10] showed that centres accredited by both FACT and Clinical Trial Network (CTN) demonstrated significantly better results for more complex HSCT such as HLA-mismatched transplants. These data reinforce the concept that clinical improvement is driven by the implementation of a quality management system embedded in external accreditation standards, especially in the context of more complex procedures. This process also results in a wider standardization of

procedures across different countries and geographic areas, thereby contributing to providing patients with similar treatment expectations even when accessing different health management systems. A comprehensive review summarized these developments [13]. Other studies have assessed the impact of accreditation on quality and organizational aspects of transplantation programmes [1, 4, 11].

Where to Start?

Before starting with accreditation process, the HCT programme needs to be formally recognized by the institutional authorities and by competent authorities if needed. This is an important step to be entitled to assign duties and responsibilities to the key persons of the HCT programme.

The accreditation process starts with a centre's aspiration to achieve certification and subsequent plan (see Fig. 14.1).

Planning The first step is preparing a timetable (see Table 14.1) triggered on the goal to reach JACIE accreditation. The introduction of JACIE standards is embedded in an accompanying quality management system, the type of which is at the discretion of the single HCT programme [14].

Implementation of an action plan and its monitoring The second step is the preparation of an action plan detailing all the operative activities, their timeframe, the key persons, and responsibilities involved and the final objectives to be reached. Where there is a QMS already implemented by the hosting institution, the preparation of the plan of action for achieving accreditation should be organized in close collaboration with the quality office of the institution.

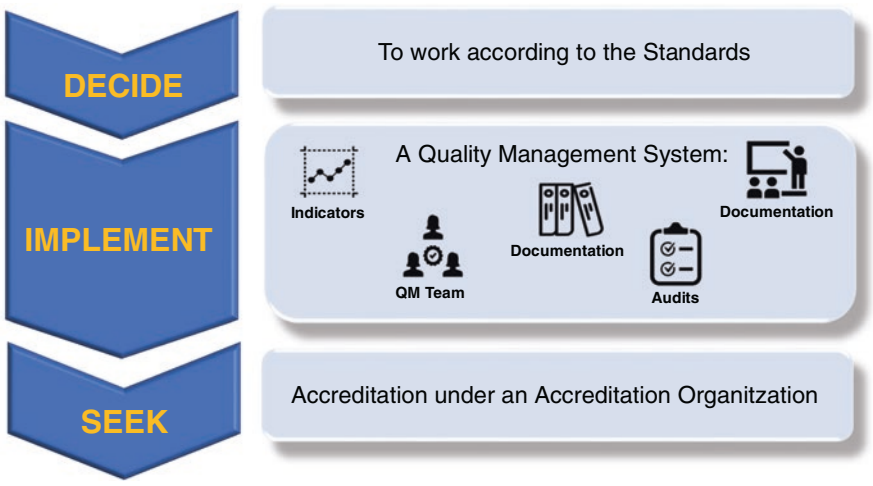

Fig. 14.1 Aspects to consider prior to starting the accreditation process

Table 14.1 Timetable

Time	Activity	Responsibility	Indicators
Before starting accreditation process	Formalization of the transplant programme	HCT programme director(s) Hospital Management	Formal institution of the HCT programme and leadership assignment
1–2 months	Preparation of the action plan	HCT programme director(s) Quality officers Working groups	Analysis of activities and processes in the light of JACIE requirements Meeting minutes of the working groups (clinical, collection and processing facilities) Finalized action plan for JACIE accreditation
12–18 months	Implementation of the action plan and its monitoring	Quality officers Working groups	Meeting minutes of the working groups Writing of the quality system documentation Staff education Audits for monitoring action plan implementation Action plan adjustments if needed
1–2 months	JACIE application	Hospital director HCT programme directors Quality officers	Upload of checklist, application form and requested documentation
3–5 months	JACIE inspection & report	HCT programme team and hospital key persons JACIE inspectors	JACIE report and checklist post inspection
3–9 months	CAPA plan post-inspection	Quality officers Working groups	Analysis of JACIE report and inspectors' checklist post inspection CAPA implementation Upload of checklist with CAPA evidences
1 month	JACIE accreditation	JACIE accreditation committee	HCT programme accreditation award

The analysis of the HCT programme processes and activities and the organization of the QMS documentation already available are the starting points to prepare a good action plan. The analytical comparison between the documentation already present and requirements of the FACT-JACIE standards enables evaluation of how much commitment must be expected in terms of personnel and working time to complete the preparation of documentation required by FACT-JACIE standards.

The action plan must also include education on FACT-JACIE standards of HCT programme staff, possibly before starting with document preparation, to enable personnel to work on documentation and on the accreditation process (awareness and competence).

The action plan must be monitored during its application so that it can be corrected and amended if necessary (action plan adjustments). The monitoring can be carried out through regular and routine meetings of people responsible of the different working groups and/or through focussed audits (on quality system documentation or on processes).

Phases of the Accreditation Process

Accreditation is the means by which a centre can demonstrate that it is performing a required level of practice in accordance with agreed standards of excellence and certify that it operates an effective QMS. According to the International Society for Quality in Healthcare, accreditation is a process "in which trained external peer reviewers evaluate a health care organization's compliance with pre-established performance standards ... Unlike licensure, accreditation focuses on continuous improvement strategies and achievement of optimal quality standards, rather than adherence to minimal standards intended to assure public safety" [12].

Programmes interested in achieving accreditation for hematopoietic cellular therapy product collection, processing and administration can contact relevant accreditation organizations, including the following:

- JACIE: www.ebmt.org/jacie-accreditation
- FACT: http://www.factwebsite.org/
- AABB: www.aabb.org

Although each accreditation organization has its own accreditation process and specifications, the following sections provide a general description of the different phases that the applicants are subject to. The accreditation process is divided into three main phases: pre-inspection, inspection and post-inspection.

Pre-inspection Phase

HCT programmes seeking accreditation are encouraged to start the accreditation process with the accreditation organization of their choice once their QMS has been in place at least for a year and there is sufficient evidence to prove compliance with the FACT-JACIE standards.

Out of the three phases of the accreditation process, the pre-inspection phase is a phase that often requires more efforts for all the involved parties: applicant and inspectors. The pre-inspection process starts when applicant submits the corresponding documentation to the accreditation organization for review and approval.

Following are the documents that are to be provided during the pre-inspection phase.

Application Form

Key information about the HCT programme seeking accreditation should be provided, including the following:

- General information: Name of the programme, contact details and invoicing information.
- Scope: Standards cover the entire HCT process, starting from the selection of the donor/patient to collection, processing, storage, and subsequent infusion and follow-up. Thus, programmes are encouraged to apply for the accreditation as a full programme, which includes the clinical unit (adult and/or paediatric), the administration of immune effector cells (IEC), the bone marrow and/or apheresis collection unit and the processing unit. However, stand-alone applications are accepted for processing units, for clinical units that work with accredited collection and processing units or for collection units that work with accredited processing units.
- Structure of the programme: Key personnel of each unit, organization of the HCT programme and distance among the units.
- Activity: Standards establish minimum activity numbers for the clinical and collection units.

The information provided by the HCT programme in the application form enables the accreditation organization to determine the eligibility for the accreditation process.

Self-Assessment Standards Checklist

Applicants need to self-assess their compliance with every one of the standards indicating if they comply or not with it and referencing supporting documentation as a proof of compliance. The information provided by the programme in the self-assessment checklist enables the applicant, the accreditation organization and the inspectors to determine the readiness of the centre for the accreditation process.

Once the application form and self-assessment checklist are reviewed and approved by the accreditation organization, the applicant provides an established set of pre-inspection documents.

Pre-inspection Documentation

This consists of selection of documents that the applicant needs to submit prior to the on-site inspection. This documentation allows the inspectors to understand the centre's activity, organization and to check compliance with some of the standards before the on-site visit. Depending on the accreditation organization (and subject to the language capabilities of the inspectors), the documentation can be submitted in

the language of the centre or only in English. Following are examples of the key documentation requested:

- Selection of key SOPs
- Evidence of staff training and qualifications records of key personnel
- Facility licences and authorizations
- Quality management plan (QMP), interchangeably referred to as the Quality Manual or Quality Handbook
- Documented evidence that the QMS is functioning
- Consent forms and related information
- Sample labels
- Plans or maps of the centre
- Sample agreements with third-party service providers

Examples of pre-audit documentation can be found at https://www.ebmt.org/jacie-document-quicklist.

Support prior to submitting the forms is available from the accreditation organization, i.e. the JACIE office. Once the application is submitted to the accreditation organization, each HCT programme is assigned to an accreditation coordinator to help and guide through the process. Also, the accreditation organizations have supporting guides to accompany centres during the process.

Completing the application form, self-assessment checklist and pre-audit documentation thoroughly and accurately leads to a more efficient on-site inspection.

During the pre-inspection phase, applicants will be requested to sign an accreditation agreement with the accreditation organization and will be invoiced with the corresponding accreditation fees.

Once all the pre-inspection information is submitted, the accreditation organization starts to assemble the inspection team for the on-site inspection. Each accreditation organization has their own pool of inspectors who are volunteers and experts in one or more of the areas covered by the FACT-JACIE standards. Inspection teams consist of at least one inspector per area to be inspected: clinical, collection and processing, one of whom is also a team leader. For example, if the applicant applies for adult clinical, collection (bone marrow and apheresis) and processing accreditation, the inspection team will consist of the following: a clinical inspector, an apheresis inspector and a processing inspector. Each inspector is responsible for assessing the standards under their area of expertise and it is the clinical inspector who is usually responsible for the marrow collection facilities. Some accreditation organizations also include a quality manager specialized inspector. When a quality manager inspector is included, they are responsible for assessing the QMS in relation to the quality-related standards in the HCT programme. During this process, both applicant and inspectors need to communicate to the accreditation organization any conflict of interest to exclude those inspectors from the inspection team. Furthermore, one of the inspectors also has the additional role of being the team leader. The responsibilities of the team leader include to provide a general overview of the interactions between the units of the programme and to become the main point of contact (among the inspectors, with the applicant and with the accreditation organization).

As soon as the inspection team is confirmed:

- Inspectors receive all the pre-audit information of the programme so that they can review and assess it prior to the inspection. During the review time, inspectors can ask for additional information and have a pre-inspection team meeting to share their preliminary assessment.
- Both applicants and inspectors start working on the inspection's agenda and the logistics of the inspection, which mainly revolves around the travel/accommodation arrangements.

Inspection Phase

The inspection phase is the most visible part of the accreditation process. Inspectors will travel to the HCT programme to verify that the information provided during the pre-inspection phase corresponds to the way they work and that it meets the requirements of the FACT-JACIE standards. The inspection is a thorough peer-reviewed examination of the aspects of the HCT programme and/or its component parts.

Inspections are conducted in the language of the centre or in English depending on the accreditation organization.

The on-site inspection consists of 1 or 2 days of inspection and comprises the following items:

- Opening meeting: This meeting is the opportunity for the applicant to present their programme and for the inspectors to introduce themselves, explain the purpose of the inspection and set a collaborative atmosphere for the inspection. It is attended by the personnel of the HCT programme.
- Review of documentation: Even though inspectors review documents from the HCT programme during the pre-inspection phase, at the time of the inspection, they dedicate a necessary amount of time to this task, looking for evidence of compliance with FACT-JACIE standards.
- Tour of the different units seeking accreditation: It allows inspectors not only to see the facilities but also to interact with the personnel working to better understand how they work on a day-to-day basis.
- Observation of a clinical/collection/processing procedure or a mock procedure: Specific observations of the procedures help inspectors to understand the process and traceability of the product.
- Interview with key personnel: It allows both applicant and inspectors to exchange key information for the accreditation. The purpose of the interview is not to assess the performance of the personnel, but it is to assess the compliance of the HCT programme with the FACT-JACIE standards.
- Closing meeting with the programme director followed by a meeting with all the programmes to highlight the observations and findings of the inspection: The

inspection team and the programme director will discuss any sensitive issues identified. Afterwards, the inspection team meets with all the personnel involved in the on-site inspection to explain the main findings and observations from each of the units inspected. The team leader takes the opportunity to explain the next steps in the process and highlights that inspectors write the report based on their observations, but it is the accreditation committee that makes a judgement on the compliance of the centre with the standards. This closing meeting helps applicants to manage the expectations about the inspection report.

After the on-site inspection, inspectors write the inspection report (see Fig. 14.2) identifying which standards are compliant and which ones need further adjustments. The inspection report is provided by the inspectors to the accreditation organization for review and it is presented to the accreditation committee (see Fig. 17.5) to decide the next steps for the HCT programme to achieve the accreditation. Once the report is finalized with the observations from the inspectors and the committee, it is provided to the applicant so that they can continue working towards achieving the certification for accreditation. The report is a fundamental part of the accreditation process.

The possible results of the accreditation report are as follows:

- All standards are compliant – In the rare case that a centre applying for accreditation complies with all the standards at the time of the inspection, the applicant will receive the accreditation without going through the post-inspection phase.
- Some standards are not compliant – The great majority of the reports reveal deficiencies and the centre needs to continue working to achieve compliance with all the standards during the post-inspection phase.

Fig. 14.2 Report pathway

Post-inspection Phase

Once the applicant receives the inspection report, they can start working correcting the deficiencies, implementing the corrective actions, and generating the supporting evidence. The degree of deficiencies identified will vary in seriousness. In most cases, it will be sufficient to provide documentary-based evidence, while in other cases, for example when the QMS is immature or facility structures are not adequate, a focussed reinspection will be necessary. Whether the centre submits documentary evidences or is subject to a focussed inspection, the same inspection team that participated in the inspection phase will assess the adequacy of the corrections. When those are assessed as compliant by the inspectors and are approved by the accreditation committee, the applicant is awarded with accreditation.

Some accreditation organizations are assessing how to offer a stepwise accreditation programme for programmes in low-to-middle income countries (LMICs). The main concept is to help centres to achieve full accreditation in different stages, which makes the accreditation goal more reachable. Programmes subject to the stepwise process must achieve the same level of compliance as programmes going through the full accreditation process, but they can do it more gradually over a longer period. This stepwise programme would allow LMIC to connect with an international network focussed on quality in HSCT and could also serve to stimulate local authorities to support accreditation in the interest of patients and donors.

Plan the Post-accreditation Period

Maintaining JACIE accreditation is probably as challenging as being awarded it first time. JACIE standards are not something that should be forgotten about until getting ready for the next accreditation cycle. The effort in the post-accreditation period is to maintain an up-to-date QMS, making the FACT-JACIE standards a part of the everyday life of the HCT programme.

Any system, without maintenance, is destined to deteriorate, including adherence to key aspects such as the QMS that depend on the possibility of changes in many aspects in the internal institutional and external health care systems. The continuous improvement of the QMS is not a simple update of the documented information over time but also means maintaining all elements and ensuring implementation on everyday working practices.

- *Documentation* including SOPs should continue to be updated and developed.
- *Audits* should continue to be planned and carried out.
- *Information* about JACIE developments should continue to circulate among the team.
- *Regular meetings* on the run up to the next inspection should continue.

- *Continuous education* of HCT programme staff should be planned and guaranteed to maintain competent personnel over time who are able to operate on programme processes.
- *Monitoring* the HCT programme activities and processes through suitable and relevant indicators (key performance data and outcome analysis) should be planned and performed at least annually.

Prompt and accurate *collection of occurrences* (this term refers to errors, accidents, deviations, adverse events, adverse reactions and complaints deviations) should be maintained and the need for CAPA plan should be investigated.

If you do not continue to develop and maintain JACIE, most of the hard work in achieving accreditation will become redundant and you will find yourself back at the beginning when applying for reaccreditation.

Key Agents

This peer-reviewed accreditation process is possible, thanks to volunteer professionals in the field of HSCT, who devote their valuable time and expertise to contribute, promote and implement quality in the transplant community: inspectors, accreditation committee members and cellular therapy standards committee.

Inspectors

Inspectors are involved in the three phases of the accreditation process (see Fig. 14.3); thus, they dedicate their efforts and knowledge to learn about the applicant and visit their programme to assess their compliance with the standards. As

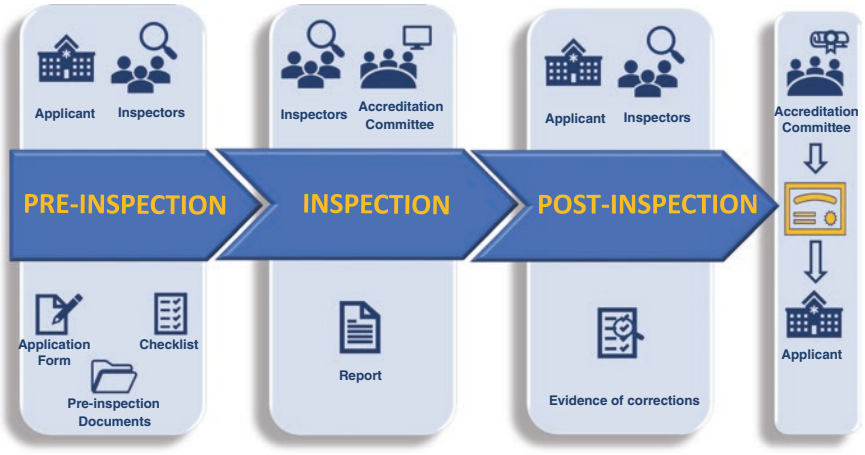

Fig. 14.3 Accreditation process flow, documentation and key agents

previously mentioned, they are the eyes and ears of the accreditation committee and include all their findings in the inspection report. Inspectors are also involved in the review of the evidence of corrections during the post-inspection process, and thus they follow the progress of the programme from the application until they achieve certification of accreditation.

The entire process is usually performed in a collegial and positive atmosphere and is often a learning and rewarding experience for both inspectors and applicants. In addition, inspectors benefit from meeting and collaborating with colleagues while helping to implement and promote quality in the transplant community [9]. Accreditation organizations might offer specific benefits to their volunteer inspectors, such as discount in the application fees of the inspector's centre or educational events.

Professionals from HCT field interested in becoming inspectors should contact the accreditation organization to learn more about the requirements. Inspector requirements are based on professional experience, completion of an inspector training course and associated exam. Before becoming an inspector, candidates must participate in the observation of an inspection.

Accreditation Committee Members

Accreditation committee members are the main source of expert opinion and peer review. Membership is formed by experienced inspectors from all the areas, clinical, collection and processing, and some accreditation organizations also include quality managers members. The accreditation committee members meet regularly to discuss the inspection reports, determine the next steps for the centres to achieve compliance and decide on the accreditation of the centres.

Cellular Therapy Standards Committee Members

Members of the cellular therapy standards committee oversee establishing, maintaining and reviewing the standards. Members are usually experienced inspectors and members of the accreditation committee.

Standards are reviewed periodically and are subject to a public consultation process before the publication of the final version.

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Chapter 15
Data Management

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Data Management

Hematopoietic stem cell transplantation (HSCT) is a multidisciplinary and definitive treatment modality for myriads of life-threatening conditions. HSCT has witnessed tremendous development and evolution since its inception and has emerged as an area of high priority. Traditionally, HSCT has been used and continues to expand as a definitive treatment for multitudes of malignancies, inherited disorders, and bone marrow failures [1–3]. This growth has been witnessed not only in the developed countries but also in low- and middle-income countries (L&MIC). Cellular therapies have emerged as the most promising treatment modalities in HCT, and this trend is expected to continue.

HSCT databases are the backbone of any quality transplant program to achieve desired end states as per the institutional lines of efforts. These registries are organized systems to collate uniform data using observational study methodology to determine trends, patterns, and treatment outcomes in HSCT. The source documents for these outcome registries are mostly the patient's medical record. Transplant database encompassing complete, accurate, and reliable transplant data is geared toward capturing evolving trends, best practices, and resource allocation/utilization and streamlining multidimensional quality indicators for continuous quality improvement (CQI) and optimal outcomes. Data management is crucial for determining trends, developing quality observational studies, and answering the

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questions that can't be answered otherwise to improve HSCT knowledge globally. Observational registries provide state of current knowledge and gaps in evidence to form the basis for prevention/intervention programs, delivery, and effectiveness. They can help in designing the optimal schema for prospective and retrospective studies and for comparative analyses of diverse HSCT strategies for HSCT vs. non-HSCT therapies. Registries are particularly useful in situations where a comprehensive and flexible research design is needed or when the purpose is to discover how a product works in a wide variety of sub-groups, including ethnicity and socioeconomic status. A hybrid approach registry collects data retrospectively and prospectively. If data collection is sufficiently comprehensive, outcomes findings from patient registries can be widely generalizable. Rapidly evolving HSCT technology and widely varied outcomes among diverse patient populations need to be balanced with data management support.

Transplant databases are aimed at monitoring the natural history of the disease, demographics, therapeutic interventions, toxicity/safety, treatment effectiveness, quality assessment, and sustainability of this high-stake tertiary care service in a systematic approach. Short- and long-term complications of HSCT require long-term follow-up of patients. Databases and the consent formats need to be approved by the Institutional Review Boards (IRBs) as per the local rules and regulations and the Standard Operating Procedures (SOPs). Data managers (DMs) play a significant role in capturing contemporary knowledge about the indications, stem cell utilization, benchmarking data quality, and assessing outcomes for better resource planning/allocation/utilization [4]. Minimal essential data on each transplant recipient and donor can be captured using EBMT and CIBMTR minimum essential forms (MED-A), and Transplant Registry Unified Management Program (TRUMP) by the APBMT, the survey form of the EMBMT, and other organizations. The HSCT database is pivotal in conducting innovative observational registry studies, providing a platform for clinical trials, and enhancing transplant outcomes. Qualified, trained, and experienced personnel are essential to initiate and maintain such registries [5]. Data managers are required for quality data management and their continuing education and training, and interdisciplinary teamwork is critical for the optimum use and outcomes of the HSCT databases [6]. Precision, communication, collaboration, and close coordination are crucial for achieving the desired end states. High-quality transplant program data management encompasses advanced methodology, operational excellence, enhanced validity, and discernable outcomes (Table 15.1). Changing trends and patterns in personalized medicine have underscored the importance of data management to ensure that all cellular products are being processed as per protocol, safety standards, and guidelines to optimize disease outcomes. Data management is a dynamic process with myriads of dimensions, applications, and deliverables as the backbone of quality HSCT program, leading to evidence-based medicine. If designed and executed correctly, it can yield huge dividends to fill in the knowledge gaps and support the center's lines of effort (Table 15.2).

Data management is pivotal for a high-quality HSCT program to identify challenges, find solutions, and overcome potential barriers to maximize clinical and patient-reported outcome measurements (PROMs). Following guidelines and

Table 15.1 Fundamentals of data management

Qualified personnel
Trained and qualified personnel
Familiarity with staging, grading, toxicity criteria
Teamwork/effective communication/collaboration/ multidisciplinary approach
Cross-training of research coordinators/data managers
Workload, proportionality, and time management
Regulations
SOPS/IPPs/by-laws, data/material transfer agreements
Accreditation for standardization (JACIE/FACT/etc.)
Ethical committee/IRB regulations
Informed consent issues
Central Institution Review Board (CIRB)
Privacy and confidentiality
Data processing
Documentation: accuracy and integrity
Source documents: case report forms (CRFs)
Harmonized forms (uniform use of standardized data elements/ definitions)
Linking data sources for efficiency
Data quality/comparability/standardization
Data monitoring safety board/committee (DMSB)
Quality assurance and performance improvement (QA/PI)/audits
Electronic data capturing (EDC): long-term follow-up data
Medical record
Electronic (EMR)
Paper-based (charts)
Hybrid
Training and in-service
Standardized data management software
Uniformity, standardization
Globally acceptable/compatible
Communication and cultural issues
Language barriers
Cultural, social, and economical heterogeneity
Cultural sensitivities/QOL instruments
Quality management
Homogeneity and uniformity of the databases
Accreditation standards: JACIE/FACT
Variation in labs/toxicity criteria/performance status (PS)
Annual review of database: new variables, biomarkers, staging/ grading

(continued)

Table 15.1 (continued)

Data utilization and publications
Overlapping registries/databases
Integration/interfacing/interoperability
Access to data
Authorship guidelines
Funding
Sustainable funding sources for long-term follow-up
Quality data generates new funding sources

Courtesy of Hussain et al. [11]

Table 15.2 Dynamics of data management in research

Benefits of effective data management
Identifying population
Fulfilling gaps in knowledge
Monitoring transplant trends/outcomes
Resource allocation – priority setting
Advocating for improved health care
Serving as a distribution mechanism
Facilitating establishment of communication network
Synchronization
Ensuring streamlined global data
Principles of data collection
Accuracy
Reliability
Validity
Simplicity
Completeness
Minimum requirements
Data collection/source documentation
Attributable, legible, contemporaneous, original, and accurate
Personnel
Regulations
Communication
Quality assurance
Funding
Data utilization/sharing/publications
Quality assurance
Standardization/accreditation
Uniform QM standards
Audits/site visits (internal and external)
Implications/outcomes of data quality

Courtesy of Hussain et al. [11]

recommendations from the CIBMTR, EBMT, WMDA, and Worldwide Network of Blood and Marrow Transplantation could be an effective way of streamlining data management issues for the HCT programs. However, following the data standards set forth by the HSCT accreditation bodies in the USA (Foundation for Accreditation of Cellular Therapy [FACT]) [7]and in Europe (Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation [JACIE]) [8] is the ideal way to promote improvement in data quality of the HSCT program from harvesting to grafting. Regional transplant registries can promote HSCT in a specific region and identify locoregional trends and practices, standards and interventions, and benchmarking outcomes. National registries can be used to benchmark transplant outcomes using the large multinational outcomes registry (EBMT, CIBMTR, EMBMT, APBMT, etc). As a reference. CIBMTR carries out an annual assessment of one-year survival post-allogeneic HSCTs in each transplant center in the USA and provides it to participating centers and the public. The globalization of patient and donor registration for HSCT is a realistic goal and can contribute to the improvement of patient care, outcomes, and donor safety. Registry data have provided valuable insights into international differences in indications for HSCT and access to HSCT. Accuracy, reliability, and validity in data management are pivotal for quality improvement, the efficiency of care, and donor/recipient outcomes. Therapeutic outcomes of HSCT are optimized by utilizing myriads of clinical indicators encompassing transparency, close coordination, teamwork, and effective communication in a multidisciplinary approach (Table 15.3). Studies have shown a significant improvement in the donor and recipient care in the accredited centers by adhering to international

Table 15.3 Strengths of HSCT databases

Excellent source of demographic and activity data – dynamic measure of patterns of care
Useful for planning intervention trials – hypothesis generation and calculating effect size and potential recruitment
"Real-world" therapeutic effectiveness and safety data (as opposed to efficacy) – compare disease management by program, region, country
Heterogeneity of standard practice across participating sites facilitates research into "best practices"
Heterogeneity among study subjects
Detection of rare consequences is satisfied by large numbers of patients followed for long periods of time – a unique advantage
Low risk to participating subjects (observational rather than interventional) can promote broad participation
Flexibility: serves as a platform for extending observation or intervention to particular groups of subjects; sub-studies
Relatively low cost to develop and maintain on a per-patient basis
Useful as a comparative arm in comparative effectiveness research
Provide meaningful data for decision-making where a clinical trial is not feasible or practical
Approximation of treatment impacts is more realistic

Courtesy of Hussain et al. [11]

standards for optimal clinical, laboratory, and auxiliary practices in HSCT [9]. The databases' value is enhanced by following the universally acceptable ethical and quality standards for the design, collection, analysis, reporting, monitoring, and auditing of the data. Scientific rigor and transparency of the registry can be strengthened by following good registry practices. Easy access of registry data to the investigators and ensuring safeguards for credible, accurate, and reliable data are cardinal elements of a quality registry. Registries must provide assurance for the privacy, confidentiality, and integrity of data.

Quality management is crucial in the operational domain of a high-quality HSCT program for optimizing patient outcomes as per the existing SOPs and playbooks for efficient, quality, and sound therapeutic yields. The minimum essential elements of data management are as follows:

SOPs/IPPS/Playbook SOPs and control measures for HSCT data management ensure the integrity, confidentiality, and authenticity of transplant data. Documentation is crucial in setting up and maintaining a quality HSCT program as per the written SOPs or Internal policy and procedures (IPPs) to ensure that each team member is aware of its roles and responsibilities at the operational, strategic, and tactical levels. The playbook is pivotal for the continuity of quality data management by underscoring techniques, tactics, and procedure of data collection, quality assurance and outcomes to optimize operations planning and execution. It highlights the importance of what, when, where, who, why, and how to optimize the process flow in a multidisciplinary approach. The playbook provides a standardized and centralized guidance to conduct HSCT data management, record data into the appropriate data management system repository, and utilize the existing outputs to analyze, plan, and forecast future requirements and best practices. It also provides instructions for accessing the data management systems and generating reports and specific instructions for data capture support.

Trained/Qualified Personnel Qualified and trained personnel with adequate HSCT experience and process knowledge are pivotal to design, conduct, and manage the registries (processing, multidisciplinary coordination, and managing regulatory issues). Collaborative efforts of DMs can help facilitate registry activities from data acquisition to data processing and publications. The data management staff are responsible for the smooth flow of pre-transplant, transplant, and post-transplant care, documentation, validation, discrepancy management, adverse events reporting, and safety as per the local and international standards.

Data Processing The scope and quality of the data collected determine the value of an outcome registry. It's critical throughout the entire life cycle of HSCT by assessing donor/recipient eligibility, screening, workup, informed consent process, HLA matching, follow-up, protocol-specific procedure, data entry, regulatory compliance, pharmacy coordination, quality assurance, risk communication, document submission, and data management of transplant patients per treatment protocols. The purpose and objectives outline the scope of the outcome registry and are

affected by a myriad of factors. Size of the registry, complexity of the data elements and outcomes collected, number of observations, and duration are essential considerations to achieve registry objectives. A core dataset of crucial variables and patient outcomes are defined by the registry to accomplish its objectives. An internationally accepted core dataset has been developed by the major outcome registries (CIBMTR, EBMT) and is recognized internationally as a model for HSCT registries endorsed by the WBMT. Case report forms (CRFs) need to be revised periodically to ensure capturing of most current data (novel biomarkers, interventions, etc.). The reliability, accuracy, and validity of data are critical elements of a quality outcome database. Data comparability is crucial for interpretation and depends on the standardization of methodology and the diagnostic criteria utilized. Robust quality control can be achieved by regular internal and external audits, monitoring, and evaluation. Good quality, user friendly, cost-effective, reliable, validated, and compatible health information systems are essential for maintaining good quality outcome databases and registries [10]. Next-generation and web-based data entry applications, with efficient data validation tools, are required to streamline observational databases. Enhanced electronic data capturing efforts with built-in auditing and quality assurance tools can be very helpful in performance improvement, research, and publications.

Cultural Sensitivities/Communication There is significant cultural, social, and economic heterogeneity globally. Such cultural sensitivities and language barriers among diverse countries in a regional/international database/trial need to be addressed. Cultural sensitivities must be considered when collecting patient-reported information, like quality of life (QOL) data. Sometimes, certain QOL tools cannot be used for sociocultural reasons. Therefore, QOL forms should be culturally sensitive and validated.

Regulatory Compliance This is pivotal for yielding high-quality outcomes of transplant data and is monitored by internal and external regulatory authorities (IRB, Sponsor, FDA, etc.). Safeguarding patient safety, privacy, and confidentiality, with dignity and respect, while on research protocol is paramount. Developing and implementing SOPs/IPPs, administrative and regulatory support, surveillance, and monitoring are critical quality indicators of the participant's privacy and confidentiality protection during collection, storage, and utilization of data. Supporting internal and external quality assurance site visits/audits, clinical review committees, Data and Safety Monitoring Boards (DSMB), morbidity and mortality (M & M) meetings, and QA committees are required elements of a quality data management program. Outcome registries and databases are often considered "low risk" in terms of the potential of harm to human subjects for being observational. Privacy concerns with regard to identifiable patient information can be addressed by registries by collection of de-identified data and collection of identifiable data for "internal use" with linked identifiers. A significant proportion of the annual HSCT performed globally use allogeneic donors acquired through a donor registry or a cord blood bank. Since most of the donor registries and cord blood banks are required to report

outcomes of products used for transplants, patient outcomes can be linked with the donor products with justification for identifiable information gathering. WHO has recommended that data collection and data analysis should be considered a mandatory part of transplantation programs following full ethical, legal, and privacy guidelines.

Pharmacovigilance Adverse drug reaction reporting, risk management, and patient safety are paramount for a transplant program and are managed by continuous surveillance, effective communication, and robust teamwork. During transplant, patient safety monitoring is a critical component throughout the transplant by precise coordination and communication among all the stakeholders.

Intellectual Property Rights, Data Utilization, and Publications Integration, interoperability, full access to each center's own data, and clearly defined authorship guidelines (based upon the number of transplants, contribution, and the center participation, etc.) are the pivotal success elements. Transplant data can be used to plan prospective HSCT trials in areas not well studied (role of geographical variations, genetic pre-disposition, genotypic and phenotypic variations, and biology of disease) by utilizing preliminary registry data. It can also be utilized to estimate outcomes and accrual patterns, sample size calculations, and implementation plans. Information about the most commonly used supportive care measures can be used to adapt protocols to standard practices and, thus, increase their acceptability in the transplant community. Comparison of clinical trial outcomes with observational outcomes can give an insight about generalizability and patient selection practices. The source of stem cells is highly influenced by chance for each patient, and in many occasions, it will not be possible to apply prospective randomization to answer some of the important clinical questions.

Funding and sustainability Collection of complete, accurate, and high-quality data is resource-intense and spans over a long period. To be sustainable over the protracted time frame, long-term financial support is required. Consideration of the intended uses of the transplant database and those sponsors who can derive value from registry information (government/non-governmental agencies, scientific organizations, research collaborators, biopharmaceuticals, accreditation bodies, philanthropic organizations, etc.) could provide additional funding support. In the context of the contract for the US Stem Cell Therapeutic Outcomes Database, the CIBMTR derives substantial funding from the Department of Health and Human Services to support its outcomes registry operations. As an outcomes registry develops robust information, it can be a rich source of data for research, and grant funding to support research represents an excellent opportunity. Biopharmaceuticals or device manufacturers may have an interest in registry data to better understand utilization of their products, and short-term projects or long-term reporting may represent a funding source. Outcome databases should remain vigilant for the innovative and collaborative research opportunities to utilize or expand the database to secure new funding opportunities.

Quality Assurance and CQI These concepts are fundamental for generating high-quality, accurate, and reliable outcomes. Quality Assurance (QA) is the best way to determine process deviations and non-compliance. Quality transplant data has minimal unknowns or missing variables and acceptable levels of procedural deviations per regulatory requirements specified for transplant program. Periodic QA site visits and audits conducted by the regulatory authorities and accreditation bodies ensure compliance, safety, and optimal outcomes. The accreditation bodies for HSCT in the USA and Europe (FACT, JACIE, etc.) mandate that transplant centers collect and utilize standard core dataset defined by the field to analyze and understand their program quality. The built-in internal and external audit process for continuous quality improvement (QQI) is one of the best practices [11]. Quality maintenance of an HSCT center warrants added personnel, IT support, strategic, and risk communication. Quality management in HSCT can optimize survival outcomes by improving transplant practices.

Conclusion

HSCT has emerged as a definitive treatment for a myriad of inherited and acquired hematological malignancies and solid tumors. Data management is a core competency and one of the crucial components of the HSCT program that encompasses initiating and maintaining an institutional transplant database to augment data collection, analysis, and spearheading the research. There is a growing need to adopt the best data management practices for high-quality transplant data infrastructure to determine trends for QI and the most advanced therapeutic option to optimize health outcomes (engrafting, toxicity, and survival outcome) and benchmarking. Accredited and standardized databases can provide highly valuable information and research data that cannot be obtained by other research methodologies. Existing international models are an excellent resource for adopting best practices in maintaining data management with advanced standards and capabilities. The standardization of data quality is critical to ascertain the scientific credibility and function of outcome registries. The World Health Organization (WHO) recommendation to mandate data collection on guiding principles on cell, tissue, and organ transplantation has been a significant new development. The data collection and analysis would be an integral part of therapy and an obligation rather than a choice for transplant centers and will be a requirement for HSCT program accreditation. The program data standardization is vital to ascertain the scientific credibility and reliability of a transplant program.

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Chapter 16
Maintaining the Quality Management Program

Nick van Sinderen

General

In this chapter, we will take a closer look with a global view on the design of a quality management system. Many standards originated a long time ago, including the FACT-JACIE standards. The FACT-JACIE standards were created to satisfy an unmet need, viz., to standardize the quality of care for patients and donors in a field of medical intervention that had high mortality and morbidity rates and operated across international boundaries. We have now arrived in a time when quality management has become commonplace and many things have become much more regular. We even have to watch out that the various quality management systems not to overlap leading to unnecessary duplication. But do we? If you compare three well-known standards such as

JCI, ISO15189, and JACIE, you already see in the general topics that there is overlap. Every single QM system has requirements on documents, education, adverse events, changes. And of course the new CAR-T treatments where JACIE is already very advanced but has to deal with regulations coming from pharmaceutical companies that are GxP based (Good Scientific Practices, where "x" stands for any of the following: M, manufacturing; L, laboratory; T, tissue; D, distribution; C, clinical; PV, pharmacovigilance). Altogether, this puts considerable pressure on hospitals and their staff. So we are no longer setting up a QM system from scratch but trying to find a way in existing QM systems where we need to combine all of them in order to protect our departments from duplication of the same rules and regulations from different standards that are often mandatory by law. Maintaining a QMS is about to become an art. It would be good that the organizations would come

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together to discuss the topics and make sure they are complementary so that valuable time can be saved which in the end is beneficial for the patient.

Establishing and maintaining a quality management system is easier said than done. It requires a lot of time, energy, and full commitment of everyone involved, starting with the (top) management. The time involved may be several years, depending on the scope (part B, C, D of the FACT-JACIE standards; see Fig. 16.1) and the clinical activity (autologous and/or allogeneic transplantation in adults and/or pediatric, cellular therapy) of your system and the starting point. The most important pool of knowledge, however, is the education, training, and experience within the team(s). All standards are initially created by colleagues in the field and, at least for FACT-JACIE, also further developed in the 3-year review cycle.

It all starts with the organization wanting to implement a QMS. Firstly, this ambition cannot have any result without the full support of the top management and the (medical) staff and all supporting staff including all other operational managers. Secondly, it sounds obvious, but your starting point is the knowledge and experience of your employees. A quality management system is there to help you organize it. Compare your own point of view with the standards and you will see that mostly you think the same. That shouldn't be that much of a surprise because the standards have been set up and developed by colleagues in the field. Starting from your own professional point of view keeps you alert and will eventually increase the level of the standard. Blindly following the standards will not.

When team members are assigned tasks in the maintenance of the system, it always goes alongside their primary work. One of the statements a department can make in the policy is that everyone is responsible for the QMS and gets smaller or bigger tasks assigned alongside of the quality manager, next to their primary tasks. This could be a responsibility for a specific document, participating in audits or maybe implementing an improvement if it is the field of expertise. There are so

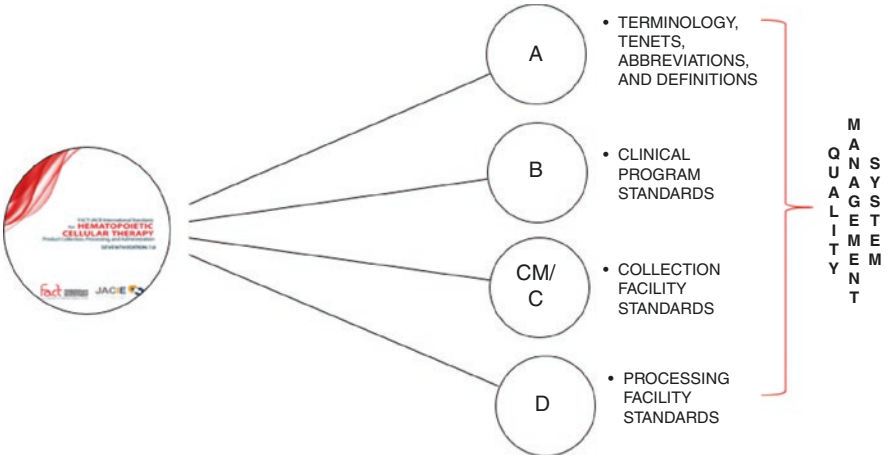

Fig. 16.1 FACT-JACIE standards, their parts, and QMS. (With permission from EBMT)

many examples in organizations, which you will recognize, where there is no time for these extra tasks. One of the reasons for that is that the number of colleagues involved are too limited and QM tasks are many times last on the list. You can prevent this by making the number of colleagues involved bigger so that they only have one internal audit per year or have to update just a few documents instead of 20 per year. A secretary can be involved in checking transplant data because he or she provides a lot of the input during their daily work, for example by creating and maintaining files. The advantage of this approach is that you reduce the pressure on your department, the medical team, and, therefore, also the patient. If you go one step further, you can use your QMS for education. Team up experienced with less-experienced colleagues in every topic and you will see in the long term that many can perform the same tasks. You will create continuity and less dependence on just a few key staff.

The Setup of the Quality Manual

Here you describe your organization, policy, scope, communication, collaborations, the treatments you offer, education, and so on. Furthermore, you address the topics in a general way linked to documents that go further into detail. Fortunately, the times when the quality manual was hefty tome, that included many or sometimes even all SOPs, are almost gone. The organizational chart (both of the department and the HSCT), shows you how the communication is setup between the facilities. Also, the position of the quality manager relative to the program can be identified here. You see everywhere in the standards that the clinical program director (CPD) is ultimately responsible for everything and must have oversight at all times. But how can this be done in practical terms? By making sure the CPD gets this information in the monthly, quarterly, and annual reports, by discussing with them regularly, including minutes of meeting, and by generating an end-of-year report that is approved by the CPD, you can cover this. It is impossible to have the CPD view every single item but it is possible to give a general overview with the ability to dig deeper when necessary. Make this visible in general in your quality manual and refer to the underlying SOP.

Work Area

The locations of parts of your scope define a large part of your logistics. This has an influence regarding your equipment, transport of cells, communication, and so on. It is not uncommon that parts of the HSCT chain are also a part of another department (for example, oncology or the HSCT lab is part of a bigger lab). Experience also tells us that in a small site, communication is likely to be good because the colleagues are used to really short lines and usually know each other very well.

However, you may see this closeness and familiarity reflected in an out-of-date documentation, and in external audits, it may appear that your document management is poor, even though everyone knows exactly what to do. What is missing is the engrained habit of documenting what you do.

Material and Supplies

It is good to see more and more that hospitals have a general way of buying goods and equipment that are validated by the manufacturer and/or during a first (test) use. Does the equipment perform like we want to? Reports and contracts are kept in a general system. Maintenance is often done internally but sometimes also by specialized companies. For these critical items, it is important to clearly describe how you deal with urgent situations regarding backup and response time agreements with the supplier.

Hygiene

In an environment where HSCT is performed, normal cleaning is not enough. Extra hygienic measures require specialized cleaning methods. This can vary between hospitals and includes the patient rooms with air and water filtering. Analyze what information your hospital already has on cleaning methodologies and routines and add what you as a department find necessary with the help of the JACIE standards. By involving the hospital-wide responsible person, you will achieve a good and natural flow in the way you work and learn from each other. The result will be an extra paragraph in the hospital-wide protocol or an additional hematology protocol with a reference. It can be expected that collaboration will build up shared knowledge. Make sure to train your staff on how it is arranged.

Education

You need the right people to do the work. Their education and experience are the basics. Educational sessions (meetings, on the job training, courses, reeducation after longer leave, congresses, participation in the development of documentation) ensure that continuous education is secured. Describe what is addressed in the initial training program, also termed “introduction,” for new employees. A good educational policy where colleagues see that their annual improvement is facilitated is very motivating. Encourage them also to write down and implement their plans and maybe even send it as an abstract to congresses such as EBMT. It is a great way to recognize their work.

Documentation

All the information mentioned is kept in the famous standard operating procedures (SOP). We have lots of them. The key trick is to make sure that SOPs are relevant and don't overlap with other internal SOPs or maybe general ones that are used in other departments or even across the hospital. Another challenge is also who to assign to be an author, reviewer, or authorizer. More on that topic is discussed in Chap. 3 on documentation.

Changes

Changes are a consequence of the analysis of outcome, adverse events, audits, trends, and daily experience. How to implement changes can differ per case. A standard analysis of influence and impact – even a small one – is recommended. A process that records and documents any changes using a *change control approach* is strongly recommended, incorporating where necessary a risk assessment of the proposed change (see Chap. 18 on risk management).

Validation

The FACT-JACIE standards define validation as, "Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications." In order to achieve the aims of validation, you need to know how your processes and methods perform in order to improve and be specific in what to improve. Validation is a tool that helps. You can divide this for example in validation of your equipment. For instance, does the apheresis machine perform within the operational parameters provided by the manufacturer? What objective measures can be used to confirm conformation to the anticipated operational parameters? For example, for an apheresis device, the harvested cell dose based on pre-harvest predictors could be a target. This is comparing expectations against real performance. How do you validate your process? That is more difficult because you need to trace the patient from the first visit until discharged from hospital. Nevertheless, if you combine your documents (electronic), patient file, and all related topics, it is possible to achieve the aim. This is teamwork! By tracing the completed patient pathway, every aspect of your process should be covered. As a suggestion, take five differently diagnosed patients per year and trace their routes and you will uncover any gaps that might be there. You could call this a process audit or a prospective risk inventory ("what if?"). The validation of your methods would be, for example, how you handle your protocols or audit cycle.

Information and Communications Technology (ICT)

The ICT process is usually covered by the hospital systems in general, and therefore it is always a challenge to get a good grip on this area. It is not uncommon that more systems are in use even sometimes in the same department. And because the HSCT chain can cover more departments, you can run into this problem. Together with the other departments and the ICT department, you need to find a way for good communication and fine-tuning. For instance, there may be more than one document management system, different processes in adverse events, different colleagues responsible, and so on. Solutions for deficiencies on this topic mostly start with the upper management in deciding how the process is changed. Due to the many responsibilities and complicated multiple systems managed by the ICT department, you really need to make a solid case on why implementing changes are necessary. Finally, a contingency plan in case of a general ICT system shutdown is an absolute must-have.

Meetings

Meetings and evaluations shows your daily, weekly, monthly, and annual lines of communication. Make sure you describe the individual meetings well and who or per specialty, is attending. There is a never-ending discussion if you need attendance lists or not; however, a list does help a JACIE inspector quickly to determine whether important meetings such as transplant operational planning meetings, QM meetings, and morbidity and mortality meetings are attended by sufficient representation of the department. In particular, to demonstrate that the CPD has oversight, a list provides this evidence. Anything that helps during the JACIE inspection will improve the efficiency of the inspection. Where electronic patient files are in place, you can also be able to see when a treatment/patient was discussed and by whom [not a good way to have oversight]. The best thing to do is describe this in your meeting overview or the protocol related. You need to fine-tune it to your own situation and improve by your experiences.

Outcome

Analysis of treatment outcomes are done on different levels – on a daily basis and over the long term. It varies from discussing a single patient to aggregate outcome results. Together with any benchmarking schemes in your country and or via the EBMT registry, you will get a good insight into how well the program is performing.

Outcome analysis, a summary of important outcomes and review, will teach the transplant team a great deal by spotting trends and helping to indicate where to

make changes. A strong advice would be to categorize generally which sounds obvious but make sure you categorize the same as your adverse events, complaints, audit findings, and so on. If you do this for your whole department, you will be even more capable of making global as well as detailed analysis. For further details, see the chapter on outcome in this book.

Risk Assessments

Risk assessment is a crucial tool that must be a core component of any transplant and cell therapy program. Risk assessment is essential in managing change as part of change control and when introducing a new process, procedure, or therapeutic intervention into the program. The challenge is to keep the risk assessment process simple. You easily drown in too many risk assessments. Define what is important and how you want to do it. A risk assessment is also the result of a discussion about a change in treatment from which the why and how you will put in the (electronic) patient file, without saying it is a risk assessment, so partly what you do on a daily basis.

A Practical Example
In JCI, you are required to use the RSVP (reason, story, vital signs, plan) method for verbal and written communication. While implementing this in a facility, the team realized that they already did this through the electronic patient file, not realizing it was a method. The facility saw this as common sense to do so.

Again, it is important to restate that you always need to check what is already in place before implementing a "new" change. What the exact best way is you will learn during implementing and evaluating and can differ per facility.

Audits

There are many audits described in the JACIE standards (see Fig. 16.2) and they will need fine-tuning depending on the scope of your activities. Do not hesitate to combine audits when possible. They are a great tool for learning and should form part of the educational program for staff. One approach for well-funded departments is to set up a team of auditors with members of every discipline. Make teams with a focus to learn from each other. An alternative strategy is to have a small group of individuals with audit training who help less senior staff members such as trainee doctors and nurses who are given individual audit topics to prepare and present to the department. Audit experience is a mandatory requirement in many countries for trainee medical staff and provides good opportunities to gain experience not only in the audit cycle but also in presentation of the completed audit. Good audits can be

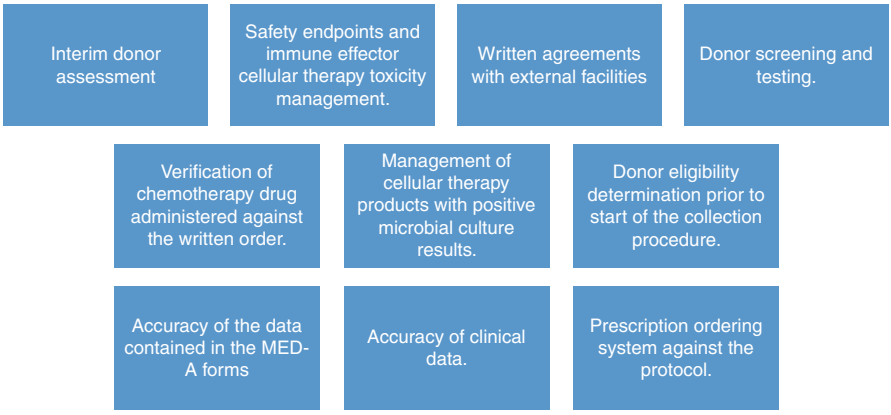

Fig. 16.2 Critical processes that must be audited. (With permission from EBMT)

submitted as abstracts to meetings such as the annual EBMT meeting. The impact that this can have on awareness of processes, who is doing what and implementing changes, is underestimated. Here are some examples of audits that must be performed regularly.

Some take aways:

- Your professional knowledge is your starting point.
- The FACT-JACIE standards are a really good helpful tool when used with the FACT-JACIE manual.
- Involve as many of the staff within the transplant program as possible in small and larger tasks, make it "their" system.
- Make teams for audits and documentation review with the aim to learn and grow.
- Appoint colleagues with a special field of their attention and give them regular opportunities during the year to present and discuss issues.
- Check what is already there, which can be used as a starting point for implementation of new things.
- Ask for input from colleagues in other hospitals who are more experienced on topics that you are not familiar with.
- Have every new colleague meet the quality manager in their initial training program so that new colleagues are familiarized with QM from the very beginning.

Chapter 17
Training Programme

Ilknur Kozanoglu and Songul Tepebasi

Cell therapy guidelines and standards, for staff training and quality control, are outlined in the European Union (EU) Directives and by other international agencies [1–5]. In addition to staff qualifications and training, the directives also require documented evidence of the qualifications of the trainers [4].

Educational activities aimed at developing staff knowledge and skills [6] are fundamental for safe and effective cell therapy. Such educational activities can facilitate the manufacturing of a cost-effective product while improving overall process and improve management. Appropriately trained staff have more self-confidence, a greater sense of accomplishment and ability to fulfil personal goals, and better communication and leadership skills [7]. High-quality and motivated cell therapy staff are indispensable regarding developing and maintaining an effective QM system. Therefore, it is advantageous for cell therapy staff to have continuous training and receive competency evaluations at regular intervals.

Types of Education

FACT-JACIE has established international standards for cell therapy, including the following training and education requirements for personnel.

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Orientation Training

This includes activities to introduce new employees to their colleagues and the treatment centre. The aim, history, philosophy, rules and procedures of the centre should be reviewed with all new staff. Information about human resources policies to include business hours, staff support services, payroll procedures, overtime requirements and benefits are provided, together with information on the physical capacity of the organisation. Specific orientation training for staff working in cell therapy should cover general therapeutic principles for each area involved in cellular therapy as well as the functionality of the cellular therapy clinical units within the centre. All training should be clearly defined in the standard operating procedures. To facilitate orientation, a handbook could be provided to all personnel to ensure compliance (Table 17.1).

Initial Training

After attending a general facility orientation, initial hands-on training of new personnel should begin. It is especially important that personnel, who will be performing critical procedures, clearly understand the work that they will be undertaking.

Table 17.1 Example orientation training programme for new personnel in a cell therapy unit

Days	Topic	Trainer
First day	Meet colleagues Roles and responsibilities Payroll and human resource requirements policy Benefits package Dress code regulations Organisation, mission and vision	Unit director Technician Personnel manager
Second day	Bone marrow centre/vision, mission, values Quality management system Organisation chart Working hours Training courses/certification Procedures/bonuses/policy violations Standard operating procedure and other forms and booklets Promotion of the hospital Transportation/housing/services Patient rights/satisfaction	Unit director Technician Quality control manager Personnel manager
Third day	General operating principles of the unit Employee, donor, patient, and product safety Workflow processes	Unit director Technician

Initial training should focus on relevant scientific and technical material, organisational structure, the QM system, health, and safety rules, and ethical, legal, and regulatory policies [4].

Moreover, the initial training should allow sufficient time to grasp the concept and application of the treatment processes at various interval of patient care. For processes where minimising error is critical, training should be repeated, at specific intervals with assigned knowledge and skills sign-offs, to ensure that personnel fully comprehend the content.

Continuous Education

Continuous staff training, both personally and professionally, is essential to ensure that both staff and the department keep abreast of the latest developments in cellular therapy [4]. Centers can develop and apply their own continuous education programs or use methods based on international standards. New developments in cell therapy occur constantly, and training will facilitate the adoption of new methods and processes by personnel. Continuous training is a dynamic process that ensures that the centre itself is committed to continuous growth and development.

According to FACT-JACIE, key personnel should participate in a minimum of 10 hours of educational activities related to cell therapy annually, and continuing education should include, but not be limited to, activities related to hematopoietic stem cell therapy. Appropriate continuing education activities [4] include the following:

- Annual meetings of professional societies presenting information which is directly related to cell therapy
- Presentation of papers at scientific meetings
- Participation in webinars and online tutorials

Training Methods

Theoretical Education

All cell therapy centres should provide theoretical training with a predetermined purpose, method, and content (Table 17.2).

Table 17.2 Planned training to be delivered over a 6-month period in a clinical unit

Center name			**(Year)**					**Date:…/…/……**			
								Page number:			
								Revision no.:			
								Revision date:			
								Application date:			
No.	Subject	Date	Place	Duration	Trainer	Trainees	Aims and objectives of education	Method and material of education	Training assessment (compatency)		Date of training
									Method	Qualification criterion	
1	Hematology/ oncology patient care	……	Clinical unit	60 Min	Transplant doctor	Stem cell transplant nurses	To raise awareness	Oral presentation	Exam	80	
2	Recognition of cellular theraphy and emergency Management	……	Clinical unit	60 Min	Senior nurse	Stem cell transplant nurses	Rapid control of complications	On-site training	Observation	Not avalaible	
PREPAED				APPROVED				QUALITY MANAGER			
Name and surname :				Name and surname:				Name and surname :			
Title:				Title:				Title:			
Signature:		Date		Signature:		Date		Signature:		Date	

Practical Training

Mistakes made during cell therapy can be fatal to patients and may also lead to product loss. Thus, practical training should be provided to personnel involved in all relevant procedures but especially those considered critical.

Rotation Training

Rotation of personnel between departments and roles will enhance experience, skills, and knowledge. The aim is to familiarise employees with the functions, rules and procedures of all departments included in the rotation cycle. Rotation training constitutes a holistic approach to the training of new personnel, who will engage in activities involving a variety of disciplines.

Conferences

Given the rapid advances in cell therapy treatments and methods, information exchange at the international level is essential to remain up to date. This can be accomplished through attendance at relevant courses and conferences.

Case Training

Case training requires personnel to analyse cases, identify problems and discuss possible solutions with their colleagues; this process allows personnel to readily apply their knowledge and skills.

Online Training

The information and technologies available through the internet have become indispensable tools for modern education. Online training has increased dramatically due to ease of access and the possibility of training many people in a single session. In addition, participants can provide feedback and their proficiency can be assessed automatically [8].

Standard Operating Procedure (SOP) Training

Cell therapy personnel should be familiar with the SOPs in a QM system. Personnel should be trained in the use of these documents so that they can be effectively applied, when needed.

Unplanned Training

Unplanned training may be required to address repeated errors, following an inspection by an auditor, or in response to events occurring on a particular day. The location and timing of unplanned training are inherently undefined but should be recorded by the QM system, as required.

Trainer Qualifications

The most important factor in the effectiveness of training is the trainer. International standards for cell therapy do not specify the qualifications required by a trainer. However, he or she should have sufficient skills, experience and knowledge of the topic to be taught and should be able to demonstrate specific competencies on request by auditors. Centres should not only employ qualified educators but also define their own training methods according to their QM plans. The effectiveness of the trainer should be assessed using a survey of training participants.

Determination of Training Needs

The training of personnel starts by determining their needs. The required training should then be delivered in accordance with legal and institutional requirements. The training required for maintenance of unit activities (e.g. SOP training) should consider not only what is needed to perform the tasks required by that unit but also the necessity to develop new skills [1–4].

The types of training needed by employees can be assessed by means of surveys, interviews, observation and performance tests. Ideally, a training commission should be created by each centre to determine training parameters including duration, location, method and certification (Table 17.2).

After training needs have been determined, a training programme should be planned and discussed with trainers. Decisions should then be made regarding who should participate in the training, and its format, delivery date/time and location.

Training programmes should be run once or twice a year, although this will depend on the identified needs and capacity to deliver training. All training should be operationally and clinical focused on the cellular therapy programme.

Documentation of Training

As discussed above, training should be conducted in accordance with the training programme. If a training session does not take place in accordance with the plan, the reason for this should be documented; postponing the session until the next training period should also be considered.

All training activities should be documented in accordance with the QM system. Every stage of the training procedure should be recorded and archived, according to the regulations and standards of the individual centre.

Training Evaluation

Evaluation of the quality and outcomes of training are essential to assess how much information has been imparted to personnel. Clear and quantitative assessments facilitate determination of the effectiveness of the training.

The criteria used in training evaluations should be defined in the training plan. Significant work aimed at quantifying the learning that occurs during training has been carried out by Kirkpatrick, who assessed four different areas: (i) participants' responses to education, (ii) learning efficacy, (iii) participants' behaviour after training and (iv) training outcomes [9].

The optimal methods for evaluating training outcomes for key therapy personnel should be determined to ensure patient/donor/product safety. Indirect evaluation methods, including product effectiveness and patient outcomes, can also be used.

In addition, training sessions should be recorded to allow subsequent evaluations thereof, whether by testing or observing the participants.

Conclusion

Training is a critical part of any QM system and can contribute to continued progress in the field of cell therapy. International standards have defined the training required for key cell therapy personnel. Within this framework, all centres should establish their own procedures for conducting and evaluating training. The procedures should be dynamic and meet the needs of the individual unit.

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Chapter 18
Risk Management

Joaquim Vives and Judit Amposta

Abbreviations

CAR	Chimeric Antigen Receptor
CQA	Critical Quality Attribute
EBMT	European Blood and Marrow Transplantation
EMA	European Medicines Agency
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FMECA	Failure Mode, Effects and Criticality Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
HLA	Human Leukocyte Antigen
HSC	Hematopoietic Stem Cells

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ICH	International Conference on Harmonization
ISCT	International Society for Cell and Gene Therapy
ISO	International Organization for Standardization
JACIE	Joint Accreditation Committee of the ISCT-Europe & EBMT
MSC	Multipotent Mesenchymal Stromal Cells
PHA	Preliminary Hazard Analysis
QbD	Quality by Design
QC	Quality Control
QoL	Quality of Life
RD	Related Donor
RRF	Risk Ranking and Filtering
SOP	Standard Operating Procedures
UD	Unrelated Donor
US	United States

Defining Risk in Cell Therapy

A risk is defined as a combination of the probability of occurrence of harm and the severity of that harm [1]. It is recognised that complex processes are involved in cell therapy embracing a life cycle that encompasses people, facilities and equipment, reagents and materials, documents, and procedures. The risk of altering any critical quality factors related to safety (that is, for any of the stakeholders involved) and efficacy of the cell-based product administered to patients need to be taken into consideration in order to improve established workflows and pursue better therapies. In our context, major risks to be considered are those affecting the health of donors and patients, so all efforts should focus on the identification of risks that may critically impact on their health and the cost of cell processing to make improved therapies affordable. Fortunately, existing pharmaceutical standards, such as GxP (Good Scientific Practices, where "x" stands for the following: M, manufacturing; L, laboratory; T, tissue; D, distribution; C, clinical; PV, pharmacovigilance), already developed tools for risk management that can cover not only the critical quality attributes (CQA) of the cellular products but all the activities involved in the entire process, from the procurement of starting material from donors to the administration in patients and their follow-up, that is "from vein (of donor) to vein (of patient)" [2–4].

The advent of a new generation of cell-based medicines, in which cells are substantially manipulated, even genetically (e.g. MSC, CAR-T cells, iPSC), poses major risks and therefore robust methods need to be established and validated to ensure safety consistently [2, 5–7].

The Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee of the International Society for Cell and Gene Therapy (ISCT)-Europe & European Society for Blood and Marrow transplantation (EBMT)

(JACIE) have published guidelines that incorporate risk-based assessment as a key element to consider in every critical decision [8]. However, it is important to note that the acknowledgement of risks does not make an unsafe or a low-quality product into a safer one. In other words, risk assessment is useless unless a proactive attitude and willingness to make a (positive) difference exist. This means that risk management is not adding an additional documentation burden but a critical quality tool that holds the potential to assist us to better understand the weakest points of processes involved in the life cycle of cell therapy treatments. Then, improvements can be implemented upon accurate documentation of processes, analysis of risks, and definition of suitable actions for mitigation. Several other factors must be taken into consideration, ranging from the design of facilities and the manufacturing process to adequate personnel training and efficient documentation system, to name a few [3]. The main goal of following a risk-based approach is to improve decision-making and lead to a more effective and efficient management and oversight framework, as well as optimal use of institutional resources.

Quality risk management (QRM) is a tool recognised and incorporated in mandatory and voluntary accreditation schemes, GMP being the strictest standard in this regard [8]. GMP is of mandatory application in drug manufacturing and, therefore, they are also applied to substantially manipulated cell-based products, which are considered medicines by most regulatory authorities [6, 9]. QRM is in fact the adaptation of the topic Q9 from the guidelines issued by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This is the major guideline providing principles and examples of tools for QRM that can be applied to different aspects of pharmaceutical quality. Importantly, ICH Q9 provides advice on the use of QRM considering that the level of effort and formality must be in accordance with the level of risk [1].

Guideline ICH Q10 (on the pharmaceutical quality system) establishes the structure to build an effective pharmaceutical quality system to support pharmaceutical development and manufacturing across the product life cycle incorporating QRM as a facilitator agent. Here it is important to note that the earlier we start considering risks, the better the management of processes could be expected in the future and, subsequently, this would lead to safer treatments. Likewise, voluntary accreditation schemes (e.g. FACT-JACIE, ISO9001) incorporate QRM, thereby showing some similarities and/or equivalences between standards [8].

The Quality Risk Management Process

In cell therapy, QRM can be defined as the systematic process for risk assessment, risk control, risk review, and communication of the quality risks in the processes involved during the entire life cycle of the treatment. A standardised and robust system is needed to identify risks, determine their potential hazards, and reduce or eliminate those that are unacceptable.

According to current FACT-JACIE guidelines, the identification of a risk can be made by providing a description and establishing the context or scope, so all the possible risks are identified and the possible ramifications or impact in all areas are analysed thoroughly [10]. Once the context or scope has been established successfully, the next step is identification and evaluation of potential risks by either source or effect. During source analysis, the source of risks is analysed and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis, the effect rather than the cause of the risk is analysed. Once the risk has been identified, it must be assessed on its potential criticality or on their likelihood of occurrence and the potential impact by either quantitative or qualitative evaluation, as shown in Table 18.1 and further described in this section.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects, and magnitude of risk under different scenarios. Risk Evaluation and Mitigation Strategies (REMS, in the USA) or Risk Management Plan (RMP, in the EU) may include (but are not limited to) detailed procedures for providing education and instructions to personnel involved (including donor and patients), monitoring patients, managing adverse events, and reporting outcomes to manufacturers. Once the risk assessment is established, an RMP can be developed and implemented. It comprises the effective controls for mitigation of risk. Risk management involves the justification and rationale for accepting risks and how to manage their impact if applicable. This can often be established in a simple one-page document for change with low impact and risk.

The QRM must be integrated into the pharmaceutical quality system to be properly documented and become a consistent tool for improvement. Risk management must be proactive rather than reactive, and it must be incorporated into the culture of prevention of the organisation. One could say that the process of QRM takes the steps depicted in Fig. 18.1, which are taken from current GMP [11] and further discussed next.

Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessment begins with a well-defined problem description or risk question. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. The document reflecting the risk assessment can be completed by following three successive steps, as described next.

Step 1: Risk identification The purpose of this phase is to recognize and record the risks of the situation being evaluated, identifying the origin of the risks and their causes. It aims to answer the question: What could go wrong? Risk identification

Table 18.1 Methods commonly used for identification of risks

Method	Objectives	Pros	Cons
FMEA	FMEA identifies, analyses, and prevents potential failures, as well as their effects and causes	Method widely used in different sectors If used prospectively, it may highlight shortcomings that had not been previously contemplated It is more objective than other tools if severity, probability, and detectability are categorised precisely	Not useful for very complex processes. If this were the case, specific steps should be selected
FMECA	FMECA takes FMEA process one step further. Each failure mode is assigned a severity level	The FMECA team will not only identify but also investigate potential failure modes and their causes being able to prioritise their importance	Not useful for very complex processes. If this were the case, specific steps should be selected
FTA	FTA identifies the possible root causes of a failure or unwanted consequences, to prevent recurrence The results of the analysis are represented pictographically in the form of a fault mode tree using symbols and standards	Visual method Useful for complex systems If applied in the design phase, it provides an overview of the risks that can help to create requirements, before starting the process	Limited approach as it only evaluates one unwanted event for each tree
HACCP	HACCP is a preventive safety system in which every step in the manufacture, storage, and distribution of a food product is scientifically analysed for microbiological, physical, and chemical hazards	Determines critical control points in the process Allows continuous improvement and better knowledge of the processes	So far it is a tool mainly used in the food sector with great potential for application in cell therapy. It should be reviewed frequently to introduce all the changes being made in the process
HAZOP	HAZOP is a technique for identifying risks that occur as a result of a deviation of the process variables, with respect to the operating parameters of the system	Helps to identify potential deviations from normal use or design intentions The output analysis is a list of critical operations for risk management	Qualitative tool
PHA	PHA is based on applying prior experience or knowledge of a hazard or failure to identify future hazards that might cause harm and to estimate their probability of occurrence	It is most used early in the development of a project when there is little information on design details or operating procedures Simple method, easy to implement	It is only a preliminary estimate of the risks of the system. Hazards identified will require further assessment with other risk management tools
RRF	RRF is a tool for comparing and ranking risks	It is particularly helpful in situations in which the possible risks and the consequences to be managed are diverse	Good justification of filtering must be made to ensure its relevance

FMEA failure mode effects analysis, *FMECA* failure mode, effects and criticality analysis, *FTA* fault tree analysis, *HACCP* hazard analysis and critical control points, *HAZOP* hazard operability analysis, *PHA* preliminary hazard analysis, *RRF* risk ranking and filtering

methods that may be used include reviewing of historical data, brainstorming, elementary cause, and assign consequences (e.g. fishbone Ishikawa, diagram, failure mode/effect table), fault tree analysis, process map, flow charts, just to name a few.

Step 2: Risk analysis Estimation of the risk associated with the identified hazards can be either a qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (aka. detectability) also contributes to the ability to estimate risk. Risk analysis aims to answer the following questions: What are the chances (probability) of happening? What would be the consequences?

There are several methods suitable for the management of risks. From these, the next seven recognised tools are considered relevant in the cell therapy field (further described in Table 18.1).

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RRF)

Depending on the particular situation to be evaluated, one method or the other will be chosen. When the risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. The application of statistical tools (e.g. Pareto charts, histograms, Process Capability Index – CpK, dispersion graphs) together with these risk management tools helps to obtain additional information.

Step 3: Risk evaluation The purpose of this final step is to compare the identified and analysed risk(s) against given risk criteria.

Risk Control

Risk control involves the decision-making of either (A) reducing the risk or (B) accepting and managing the residual risk. Ideally, identified risks will be reduced to acceptable levels, always remembering the premise that the effort and resources applied must be proportional to the risk. It aims to answer the following questions: Is the risk beyond the acceptance level? What can I do to eliminate or reduce the risk? What is the appropriate balance among benefits, risks, and resources? Are there any new risks introduced because of the actions taken to control a risk?

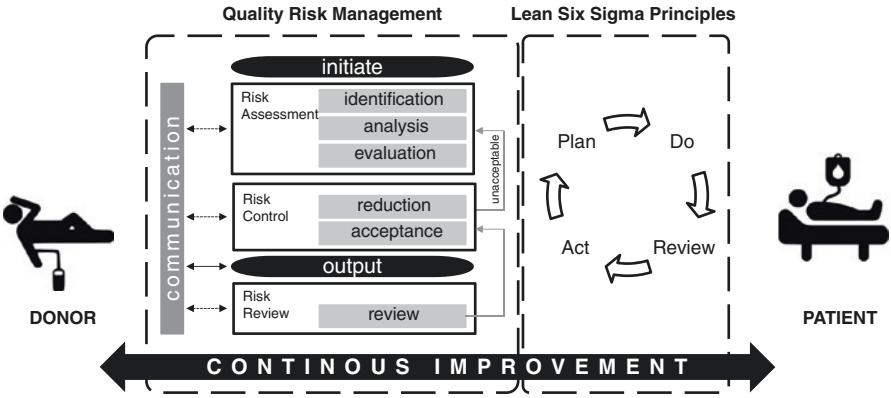

Fig. 18.1 Overview of quality risk management along the life cycle of cell therapies

Step 1: Risk reduction Here we must focus on actions to decrease severity and the likelihood of any harm occurring when it exceeds a specified (acceptable) level (Fig. 18.1). This step may imply a redesignation of the process (e.g. inadequate controls, lack of robustness of the process).

Step 2: Risk acceptance Risk acceptance is a decision to accept risk after the evaluation of severity, likelihood, and the detectability of hazards. Risk acceptance can be a formal decision to accept the residual risk (risks well specified) or it can be a passive decision in which residual risks are not specified (risks are part of the natural variability of the process). For some types of harms, even the best-quality risk management practices may not help to eliminate the risk completely, but only reduce it partially. This (specified) acceptable level may depend on many parameters and should be decided on a case-by-case basis. The rationale behind such a strategy should be documented, residual risk described, and appropriate management strategies put in place.

Risk Review

It is very important to carry out continuous monitoring and verification of risk management to identify changes in the assessed situation. This could generate new risks or affect the effectiveness of the initial risk management plan. We must be aware that the probability of risk and the risks themselves will change when the conditions change. Risk review serves as a verification and is key to promote the concept of continuous improvement. Risk review is easier to perform if there is someone in charge of monitoring the progress of the implementation of the action plan . Importantly, this step adds value to the risk analysis management.

Risk Communication

Risk communication is the act of sharing information on risk and risk management between the decision makers and stakeholders involved in critical steps of the cell therapy process (as discussed in section "Stakeholders Involved in Risk Management"), thus ensuring an effective information flow. Parties can communicate at any stage of the risk management process (dashed arrows in Fig. 18.1). The output of the quality risk management process should be appropriately communicated and documented (solid arrows in Fig. 18.1). The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for every risk acceptance. Risks which are subject to frequent changes by trend need to be reported more frequently than constant risks.

Stakeholders Involved in Risk Management

Activities involved in risk management of cell therapy processes should be carried out by multidisciplinary teams, including experts in the different areas (e.g. quality assurance, process and quality control, medical management, pharmacy) and a risk management coordinator. It is very important to establish well-defined, up-to-date standard operating procedures (SOP) and having the necessary resources. This team should meet on a regular basis to keep the risk analysis in a living state, which is updated with the latest data available (e.g. incidences, non-conformities, bio-vigilance).

Illustrative Examples of Specific Applications

Risks in cell therapy are diverse due to the complexity of the whole process and may impact on any critical step along the life cycle. A good understanding of the six Ws (summarised in Box 18.1) is key to realise the potential of risk management. Some explanatory examples are described next to illustrate the applicability of QRM and its potential to support continual improvement.

Box 18.1 The Six W of Risk Management in Cell Therapy

- *Why?* Improve safety of donors; improve survival and QoL of patients
- *What?* Identify hazards and the risk of impacting in critical steps along the life cycle of cell therapies
- *Who?* Multidisciplinary team involving quality assurance, process and quality control, medical management
- *Where?* Hospitals and processing units
- *When?* Always, being part of a continual improvement process
- *How?* Following the risk management process

Related vs. Unrelated Donors

Donation of HSC from related donors (RD) is associated with higher occurrence of adverse events (including death) than in unrelated donors (UD) [12]. Circumstances particularly applicable to RD are complex and contribute to increased risk. Risks include the lack of regulatory guidance, logistical and financial barriers, lack of the benefit of anonymity, close relationship with the transplant recipient, and the consequent pressure to donate. RD tend to be older than UD and therefore more likely to have morbidities. The impact of quality management in driving change was confirmed by Anthias and collaborators, who reported that improvements observed in donor care were successfully achieved in areas where recent FACT-JACIE standards were introduced [12]. Continual improvement can be further achieved by gradual understanding of risks, particularly present in each individual institution.

Processing of Cell Therapy Products

Cell-based therapies are rapidly evolving from traditional HSCT to current genetically engineered immune cells and mesenchymal stem cells [13, 14]. Therapeutic activity of cell-based products is susceptible to intrinsic biological variability, as opposed to traditional pharmaceutical drugs, such as small molecules or biologicals. In this context, it is crucial to deeply understand the cell's critical quality attributes (CQA) (directly impacting on the product's safety profile and clinical efficacy) and how these are affected by any disturbance in the process [15]. Moreover, cell manufacturing is a poorly automated process, prone to operator-introduced variations, and affected by heterogeneity of the processed organs and tissues and batch-dependent variability of reagent efficiency [16]. In a recent study, we reported the impact of risks associated with main failure groups (that is process, equipment, personnel, documentation, environment, reagents, and materials) on the specifications of a mesenchymal cell-based product with multiple applications including the management of acute graft-versus-host disease (GvHD) [17]. From all risks that were identified, those associated to cell processing and apparatus were high in the initial steps of product manufacturing but replaced by risks associated to operator errors at later stages of production. In this study, the risk analysis was performed following FMEA/FMECA and actions were prioritised using a simple Pareto chart, proving to be a powerful method within a clinical cell therapy manufacturing context, as well as an ideal vector for prompting alternative and proactive improvement processes [18, 19]. Moreover, the intrinsic flexibility of the method makes it ideal for critical risk assessment in all processes related to the entire life cycle of the cell-based product, thus allowing to properly identify risk priorities and corresponding control activities, supports the identification of necessary actions for quality improvement, and provides a specific model for guidance of cell transplantation centres and cell processing facilities approaching risk management for the first time, especially if lacking personnel with specific risk analysis expertise [16, 18, 19].

Patients

From EBMT registry data, Snowden and collaborators confirmed the correlation of occurrence of new centre accreditation with improvements in patient survival and reduction of procedural mortality, demonstrating the clinical benefits of adoption of quality standards [20]. Consistently, transplant centres in advanced phases of FACT-JACIE accreditation are linked to significantly higher survival rates, independent of year of transplantation or other risk factors [21]. Therefore, the implementation of FACT-JACIE standards contribute to improved processes and mitigate existing (maybe hidden) risks. In addition to general QRM, specific tools have been created as is the case of the EBMT risk score, providing a simple way to assess benefits and risks of HSCT for an individual patient pre-transplant, by assessing only five factors (namely, age of the patient, stage of the disease, time interval from diagnosis to transplant, HLA matching, and gender of donor and recipient). Higher risks are observed for an individual patient with increasing score from 0 (best) to 7 (worst) in an additive way [22]. Integration of the EBMT risk profile into the risk assessment should guide in the decision process, ultimately leading to a better decision in the selection of transplant patients.

Final Remarks

Remarkable improvements can be achieved by following simple risk assessment tools. Growing evidence shows that the systematic and comprehensive evaluation of risks impacting on safety and efficacy of cell therapy contributes to proper management of risk affecting donors and patients. Institutions already accredited for standards incorporating QRM are best positioned to drive change in cell therapy by a systematic risk-based approach. Rather than following each of the different quality guidelines and standards separately, we encourage institutions to customise their own methodology of QRM to fit them into the unique characteristics and needs of their institutions. Importantly, quality management systems need to be flexible enough for continuous evolution from traditional HSCT and stay open to the future trends in cell and gene therapy.

It should be noted that Lean Six Sigma strategies are fully compatible with QRM. In fact, some hospitals and blood and tissue banks are already using these tools and we expect this to become the trend if they both are dynamic and facilitate continual improvement in the life cycle of the treatment.

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Index

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