Chapter 13

Writing a Quality Management Plan

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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 / Programme staff	Quality Manager	Staff
Agreement	Registration XX	Responsible of Parties involved	Director (HCT Programme)	Director (HCT Programme)	Director (Facility / Programme)	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.

Clinical Unit indicators	Transplant activity indicators	Collection facility	Processing Facility
N° of inpatients/year	N° of transplants /year (allogeneic and/or autologous)	N° of potential donors evaluated / year	N° of cryopreserved procedures / year
Mean length of stay	N° of follow up examination for allotransplanted patients/year	Time from donor starting evaluation to final selection	N° of cryopreserved bags / year
Index of bed occupation	Time from donor search activation to final selection of an HSC donor	N° of donors collected / year	N° of clonogenic assays / year
Index of turnover	Time from donor search activation to transplant	N° of collection per patient	% of viability after thawing (mean)
Index of bed rotation	N° of withdrawn donor workups / N° of activated donor workup per year	cell yield per collection	CD34+ cell recovery (post processing vs post thawing)
N° of new diagnoses/year	Waiting list for transplant	duration of each collection	N° of validation procedures / year
N° of follow-up visits/year	Engraftment (time to recovery of neutrophils > 0.5 x 10 ⁹ /L and platelets > 20 x 10 ⁹ /L)		
N° of falls/year	N° of no engraftment/year		
Clinical trials indicators	overall and treatment-related morbidity and mortality (at 30 -100 days and 1 year after transplantation)	% of products with positive microbial culture results	
N° of Phase I clinical trials with active enrolment	aGvHD grade within 100 days and cGvHD grade within 1 year after allogeneic transplantation	N° of non-compliant products / year	
N° of internal audits/year			
N° of Nonconformities (product, process, service)/year			
N° of adverse events (product infusion, chemotherapy treatments) / year			
N° of complaints / year			
N° of staff training and education activity			
N° of peer review publications			
N° of SOPs reviewed / N° of SOPs to be reviewed			

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 labeling, 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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