Overview of Aide-Memoire: 'Key elements'

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ahcta alliance for harmonisation of cellular therapy accreditation

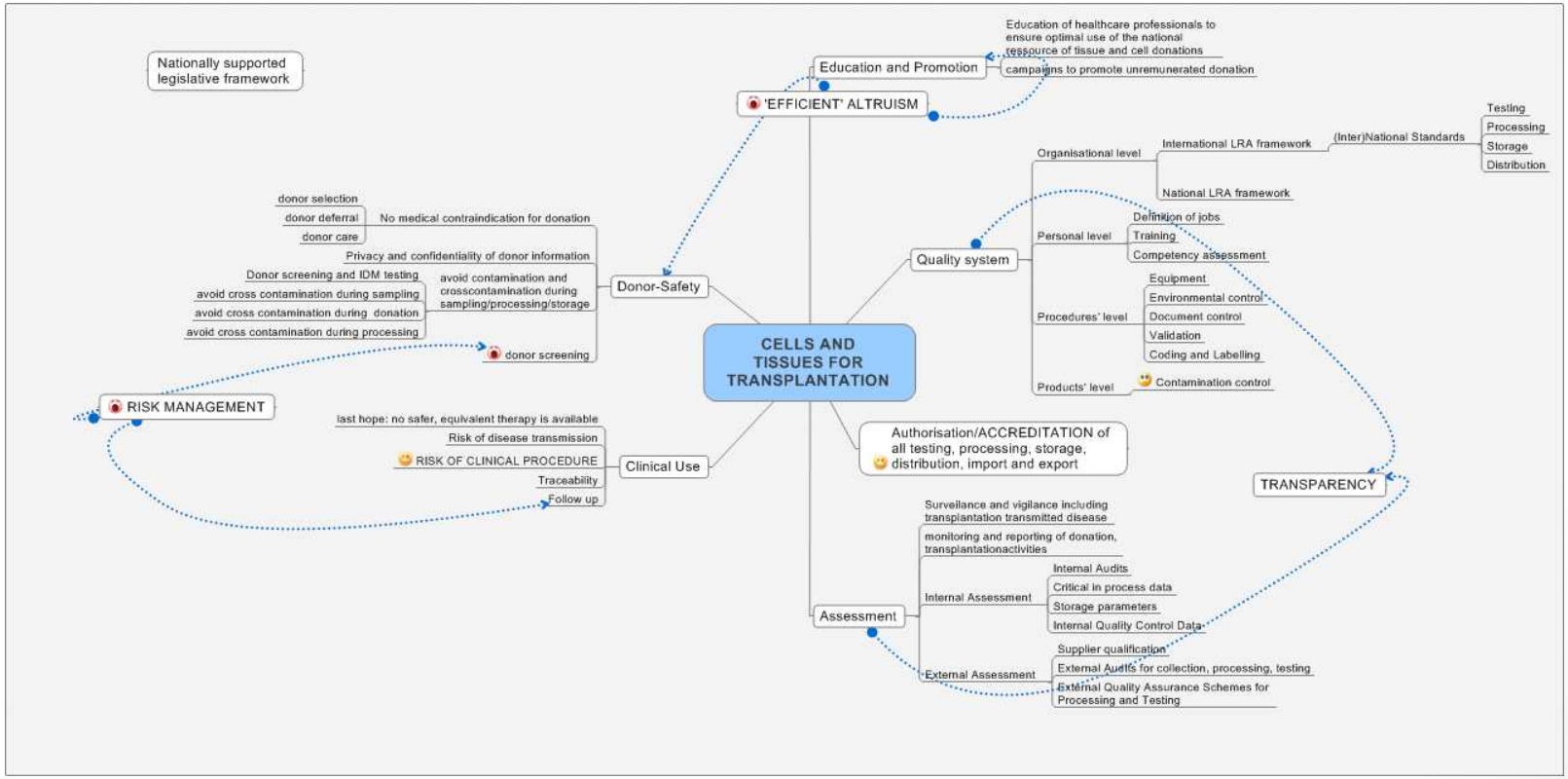
Introduction: Purpose of document

- Created as a tool to help developing HSCT programs embark on a path towards accreditation
- Does not replace accreditation or set a lower standard
- Rather, it defines the minimal essential elements of quality for new programs
- These basics provide a foundation on which to build a quality system
- Ultimate goal is to establish program that meets requirements in standards and attains accreditation

Status

- Work in progress
- About 80% finished
- **Next steps:**
  - Learn from your feedback today
  - Identify areas needing clarification
  - Share with donor committee for input on donor components
- Revise as needed
- Post on AHCTA website and WBMT website for open access

Cells and Tissue Transplantation Mind Map



Purpose of Mind Map

- Shares rationale, thinking and flow of elements
- Incorporates policies, processes and procedures (PPP's), at every level:
  - *Policies* – global statements explaining rationale; overall plan
  - *Processes* – describes flow and systems in place to meet policies
  - *Procedures* – step by step detail outlining actions to be taken

WHO Aide-Memoire on Human Cells and Tissues for Transplantation

Key Elements

1. National Oversight
2. Education and Promotion
3. Quality Systems
4. Assessment
5. Donor Safety
6. Clinical Use

National Oversight

- Legislative/regulatory framework
- Appropriate national/international standards
- Inspection and authorization of screening, testing, retrieval, processing, storage, distribution, import and export
- Surveillance and vigilance including transplantation transmitted disease
- Monitoring and reporting of donation, processing, distribution, import, export and transplantation activity data

Education and Promotion

Education of healthcare professionals to ensure optimal use of the national resource of tissue and cell donations

- Define policy and procedure for developing education of healthcare professionals to ensure optimal use of the national resource of cellular therapy products donations
  - Plan educational activities to increase awareness
  - Liaise with clinical programs
  - Collect data to monitor the optimal use of national resources of cellular therapy (CT) product donations
  - **Campaigns to promote voluntary unremunerated donation to support tissue and cell donation for transplantation**
  - Establish campaign drive as an act of altruism

Quality System

Organizational Level

- **International Legislative Regulatory Authority (LRA) Framework**
  - Based on respective institutional decisions to select the most appropriate international standards to meet the needs for testing, processing, storage and distribution for CT products which are imported or exported to ensure compliance with international standards e.g. AABB, FACT-JACIE International Standards, FACT-Netcord, EFI/ASHI etc.
  - Share CT product information and data e.g. product donations and transplantations, adverse events to ensure transparency

Quality System

Organizational Level

- **National Legislative Regulatory Authority Framework**
  - The organization and management should meet the relevant requirements of National/International Standards and prepare for certification by a National or International Accreditation Body.
  - Legislative and regulatory framework by a local national authority
    - To ensure consistent quality and services in the donation and transplantation of CT products, there should be a national health authority providing the legislative framework.

Quality System

Organizational Level

- **Quality management**
  - Prepare an organizational chart for each CT facility- i.e. collection, processing and clinical facilities have separate charts
  - Prepare a Quality Manual with defined quality policy, quality plan and management structure for each CT facility
  - All quality and operational policies, processes and procedures should be developed and implemented to meet national/international regulations, and annually reviewed by the management

Quality System

Organizational Level

- **Quality Manual**
  - Organization –executive management, quality system
  - Resources – human resources, staff selection, training, competence assessment
  - Equipment- selection, validation, preventive maintenance
  - Supplier and customer issues
  - Process Control for all CT- products facilities i.e. collection, production and clinical with blood and marrow transplantation activities including change control
  - Documents and Records
  - Identification and control of non-conformances
  - Assessments, internal and external
  - Process improvements - corrective and preventive actions
  - Facilities and safety

Quality System

Personnel Level

- **The collection, processing and administrating of CT products should have policies and procedures to ensure there is an adequate number of appropriately qualified, trained and competent personnel to perform, verify and manage the critical activities at each facility**
  - For each category of personnel
  - Establish detailed job description and responsibility
    - Establish initial training and training plan, including assigned specific task, infection control, biosafety, chemical safety, decontamination, waste disposal and information system etc.
    - Establish competency assessment
    - Establish continuing education plan

Quality System

Procedures Level

- **Equipment**

  Define and document selection criteria and review the specification

  - Assign unique identification number to each equipment
  - Define and document criteria for the qualification and validation of equipment (IQ, OQ, PQ)
  - Define preventive maintenance and calibration schedule for each piece of equipment
  - Define calibration policies and requalification procedures if equipment is out of calibration
  - Define personnel or vendors accountable for equipment preventive maintenance process and reviewing the reports

Quality System

Procedures Level

- **Environmental Control**
  - CT products are collected and processed in a liquid state and stored in both liquid and frozen states. Temperature control is crucial.
    - Establish critical temperature limits for product collection, transport, processing and storage
    - Establish procedure to monitor and record temperature of product or product environment at an appropriate level
    - Use temperature controlled and monitored storage devices for products and temperature sensitive materials
  - Identify manufacturer provided environmental factor limits for storage and use of materials, supplies, raw components and devices used in the collection or processing of CT products

Quality System

Procedures Level

- **Document Control**
  - Traceability of CT products from the identification of the donor to the transplantation of the CT product to the recipient is a critical issue for patient's safety and effective therapy outcome
  - There must be policies and procedures to create, review, approve, retain and archive documents and records
  - Standard operating procedures (SOP) manual
  - Preparation and validation of SOPs
  - Process for document change control that include description of changes made, approval and effective date
  - Process for distribution of controlled documents
  - Master list of documents and records including title, assigned number, version number, review /revise and effective dates
  - Process control for the use of electronic documents and records

Quality System

Procedures Level

- **Validation**
  - FDA Definition- Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes
  - Validation is required for any new or changes in:
    - e.g. Processes or procedures in CT Products facilities
    - e.g. Equipment used in CT Products facilities
    - e.g. Reagents or other critical materials e.g. DMSO.

Quality System

Procedures Level

- **Validation**
  - Components of Validation - Typical approach
    - Prepare a validation protocol for review and approval including details of the required testing and required acceptance criteria
    - Perform approved validation protocol and collect the data
    - Submit the validation report displaying a summary of all data, discussion of results and discussion of any deviation for review and approval
    - All validation documents (including printouts) must be filed and retained as per national/international regulations

Quality System

Procedures Level

- **Coding and Labelling**
  - Finished CT product labels
    - Labels must ensure correct identification by the administrating clinician as that product is only for a specific recipient
    - Label must also provide information about the product that is relevant to the clinical management and proper handling of the product
    - Maintains integrity during use
    - Remain attached or attached as required
    - Clearly readable

Quality System

Procedures Level

- **Coding and Labelling**
  - Finished product labels
    - Required data fields on label affixed to product container
      - Proper name of product class (e.g. Hematopoietic Progenitor cell, apheresis or HPC, A)
        - FACT_JACIE International Standards & AABB accrediting organizations endorse ISBT 128 label that provides uniform system of product naming
      - Description of product modification or manipulation (e.g. RBC Reduced or Thawed, Washed)
      - A numeric or alphanumeric sequence used to designate a given CT product to prevent use for another purpose. This also aids in tracking of the product and related products to the collection and manufacturing records

Quality System

Procedures Level

- **Coding and Labelling**
  - Finished product label

    Required data fields on documentation attached to or accompanying product container

    -Name of intended recipient if known

    -Secondary ID information of intended recipient (e.g. Institutional medical record number or birth dates)

    -Appropriate volume

    -Name & volume or concentration of anticoagulant & other additives

    -Product expiration date and time or recommended used by" date/time"

    -Recommended storage temperature

    -Biohazard and/or Warning labels

    -Donor identifier

    -ABO/Rh of donor is applicable

    -Date, time collection ends

    -Identity & address of collection facility or donor registry

    -Identity & address of processing and distribution facility

Quality System

Products Level

- **Contamination Control**
  - Hematopoietic cell products are handled under aseptic conditions during production to prevent:
    - Introduction of infectious agents, and
    - Cross contamination between products
    - Use of biological safety cabinet
    - Use stringent aseptic technique during production
    - Staff are trained to use appropriate technique
    - Handling of one product at a time in work environment

Quality System

Products Level

- **Contamination Control**
  - Materials and supplies
    - Use sterile materials and supplies for all production steps
    - Review of manufacturer provided documentation to verify sterility
    - Validation of sterilization procedures for in-house produced materials and supplies
    - Review of all materials and supplies for intact packaging upon receipt

Quality System

Products Level

- **Contamination Control**
  - Sterility testing
    - Testing of products after completion of production to confirm sterility
    - Investigation of positive culture results to identify the source and root cause of contamination,

    During storage
    - Products must be stored in a manner that maintains the integrity of the container
    - Storage conditions must minimize risks of product cross-contamination

Assessment

Donor screening and infectious testing

- **To prevent transmission of infectious disease, donors of HPC products shall be screened and tested prior to collection**
  - Timing
    - Donor screening and testing should be completed as recently as possible prior to collection
  - History
    - Review past medical history, past travel history , past behaviour history
  - Physical examination
    - Medical evaluation by competent health care provider

Assessment

Donor screening and infectious disease testing

- Integrity of blood samples

  Confirm blood samples are collected from correctly identified donors and blood samples not diluted by IV fluids

  - Testing of blood samples
    - Testing for presence of infectious diseases that are relevant by local competent health authorities
    - Testing is performed by laboratories licensed by local competent health authorities
    - Testing kits used are licensed for donor testing by local health authority

Assessment

Monitoring and Reporting of Donation, Transplantation Activities

- Where applicable, a registry of donations and transplant outcomes is helpful
- Provides a tool for tracking and trending of data
- Provides some data for retrospective analysis

Assessment

Internal Assessment

- Documented systematic evaluations to determine whether approved policies and/or procedures have been properly implemented and followed to ensure the quality of the final cellular products and services provided from donor screening to administration of CT products

Assessment

Internal Assessment

- **Conducting internal audits**
  - Policy and procedure for conducting internal audits at all CT-Product facilities, activities from collecting, processing and administrating CT products
  - Selection and training of internal auditors
  - Facility's QM prepares internal audit plan with checklists
  - Prepare an internal audit report with findings and plan for corrective and preventive actions
  - Follow-up with the completed corrective action reports and monitor the ongoing improved process

Assessment

Internal Assessment

- **Critical in-process data**
  - Process in place to review the daily, weekly or monthly worksheets and reports to identify unsatisfactory performance and gaps for continued improvement
  - Occurrence reports

  Internal Quality Control (QC) Data
  - The appropriate level of QC is used
  - QC is performed and monitored at designated interval
  - Corrective action is taken and documented when QC fails

Assessment

Internal Assessment

- **Storage parameters**
  - Ensure stringent aseptic procedures are used to decontaminate workbenches
  - Ensure the storage temperature of refrigerators, freezers and level of liquid nitrogen are continuously monitored by a 24 hr recording device (or 4hr manual recording) and alarm system
  - Ensure required preventive maintenance is performed on all equipment used for storage of CT products
  - All staff are trained to report unusual occurrences and actions taken to prevent repeat occurrences

Assessment

External Assessment

- **Supplier qualifications**
  - Policies and procedures are used to select the supplier of reagents and critical materials and to evaluate the quality of the materials and services provided by the suppliers
  - Policies and Procedures are used to select and to evaluate the services provided by the outsourcing laboratory services e.g. HLA, infectious disease markers testing etc. Laboratories should meet national/international standard
  - Materials are validated against the supplier`s claims
    - If assessment fails, the supplier and appropriate managing authority is notified and action is taken.

Assessment

External Assessment

- **External audits for collection, processing and testing**
  - Policy and procedures are in place to include external audits by national regulatory agencies and international accreditation bodies (e.g. AABB, FACT-JACIE International Standards, EFI/ASHI etc)
  - Enrolment in external assessments should cover scheduling, conducting, documenting and reviewing, including corrective action, similar to Internal audits.
  - Enrolment in External Quality Assurance Schemes (EQAS) for production facility and testing laboratory.

Donor Safety

No Medical Contraindication for Donation

- Donor selection
- Donor deferral
- Donor care

Privacy and Confidentiality of Donor Information

Avoid Contamination and Cross contamination during Sampling/Processing/Storage

- Donor screening and IDM testing
- Avoid cross contamination during donation, sampling and processing

Clinical Use

Last Hope: No Safer, Equivalent Therapy is Available

- **There will be an evaluation of the optimal treatment with CT products for each individual patient**
  - Identify the treatment options for each individual patient
  - Review the clinical results as reported in the literature
  - The use of CT products as part of the treatment is the last hope for the patient
  - The patient needs to know the risks and benefits of the administration of the CT products
  - A signed informed consent must be part of the patient dossier

Clinical Use

Risk of Disease Transmission

- **There shall be a system to monitor and prevent disease transmission**
- Missing undetected reactive transplantation transmitted disease markers due to narrow (latent) window period of the virus
- Unavailability of sensitive test kits to detect rare and unknown virus
- Incomplete donor's travel or behaviour histories

Risk of Clinical Procedure

- **There shall be a system in place to evaluate and prevent severe adverse events/reactions**
  - Graft versus host disease, ABO incompatible CT-products, contaminated products during collection and processing
  - Infusion reactions are common during HPC-A administration
  - A stringent CT- products administrating policy and procedure
  - The severe adverse events shall be documented, evaluated and reported to the processing facility and to the authorities according to applicable laws and regulations

Clinical Use

Traceability

- **There shall be a system in place which allows tracing of the CT product to the original donor**
  - The information on the product label must include unique information of the donation event (i.e. donor registry/donor collection centre, donor identification etc.) and details on the processing (i.e. processing center, unique product identification etc.)

Clinical Use

Follow up

- **There shall be a policy for determination of the efficacy of the CT products**
  - The clinical follow up after the administration of CT products shall be monitored and documented
    - For HPC transplant, the hematopoietic reconstitution will be measured in a timely manner
    - For other CT-products, efficacy parameters will be determined, evaluated and documented
    - When the outcome analysis indicates delays in hematopoietic reconstitution, the cause shall be examined and documented
    - The results of the patient outcome shall be reported to the processing facility and corrective and preventive actions shall be defined and executed

Thank you