JACIE Accreditation 2010 and Beyond

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Aims of this presentation
- Explain the current regulatory environment for stem cell transplantation in Europe
- Discuss stem cell storage
- Discuss recent developments in the JACIE standards, highlighting recent areas of interest
- Explore how JACIE and national authorities can work together
- Emphasise the central role of Quality Management

Advances in Cell Therapy
- Cures in patients with haematological disease
- Advances in immunotherapy of cancer and viral infections
- Application of stem cell research to solid tumours and degenerative diseases

Trends in Clinical Transplant Practice
- 50-70,000 HSCT annually worldwide
- EBMT 2005 - 27,941 HSCT reported, 35% allografts
- Europe - 52% first-time allografts from id-sibs, 41% from unrelated donors
- HSCT increased in all diseases except CML - use of imatinib
Regulation and Accreditation

- Allows centres to demonstrate performance to agreed standards of excellence
- Reproducibility and reliability of Clinical Processing Collection procedure
- Enhance quality and microbiological safety
- Ensure traceability of cell therapy products (CTPs)
- Motivate staff by setting clear goals

The Recent History of Regulatory Requirements in Europe

- 1978 – Council of Europe (CoE) resolution 78(29): harmonisation of legislation in collection and transportation of human cells
- 1994 - CoE Resolution (94)1 - identified variability of quality and safety of tissues and cells in Europe
- 1999 - JACIE established (1st inspection 2004)
- 2004 – EU Tissues and Cells Directive published
- 2006 - EU Directive transposed into national legislation
- 2007 - EU Commission Directives implemented

Timeline of Involvement of Different Organisations in Cell Therapy R&A

Voluntary Standards/Accreditation
- NMDP
- AABB
- FACT/JACIE
- Netcord/FACT
- CAP


Regulatory
- FDA
- EU

State & Local regulations

JACIE - Objectives

- To promote quality in patient care and laboratory performance in HSC collection, processing and transplantation through agreed systems of accreditation
- To allow centres to demonstrate performance to a required level of practice via agreed standards of excellence
- To work with different countries and in different languages to achieve accreditation
- To provide training on inspection practices and quality management
What is JACIE?

1. Accreditation of Individual Centres
   - Assistance
   - Inspection
   - Review
   - Reports
   - Certification

2. Information / Education
   - Information
   - QM courses
   - Training courses
   - Sample documents

3. Regulatory Issues
   - Standards
   - Regulations
   - Harmonisation
   - International cooperation

Vital to ensure consistency of standards between centres and countries

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FACT - JACIE Standards: 4th Edition

4th edition of standards implemented Jan 2009

Joint FACT-JACIE document

5th edition process commences in June

Standards - Essential Principles

- Establishment and maintenance of a Quality Management Programme (QMP)
- Requirement for documentation of policies, procedures, actions, requests which extends to all aspects of transplant activity
- Personnel must be appropriately qualified, trained in the procedures they regularly perform and competency to perform tasks after training must be assessed and documented
- Validation of all equipment and procedures

Importance of documentation
- Not just SOPs and policies
- Training records
- Written criteria for donor selection
- Documentation of donor suitability in recipient's medical record
- Written information to collection facility about donor
- Written request for collection or for cells for infusion
- Maintenance records
- Service contracts with external facilities
Practical guide to implementing quality management in a stem cell transplantation (SCT) programme

- **Phase 1 (completed):**
  To write and publish a guide to implementing quality systems in stem cell transplant programmes in line with the JACIE Standards on quality management.

- **Phase 2 (from 2008):**
  To update the guide on a regular basis based on continued accrual of experience and best practice.

- The project fully funded by an unrestricted educational grant from Chugai sanofi-aventis®.

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**Reason for inspection**

Questions:

- To what extent does the quality system and the organisation meet the standards?
- To what degree is the quality system implemented?
- (Is the quality system effective?)

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**Defining Inspection**

A quality inspection is a systematic and independent examination to determine whether on a level of quality and the coherent results, activities correspond with the planned measures and whether these measures are suitable and have been effectively implemented to achieve the objective.
Definition of inspection

- NOT intended for tracing faults
- NOT intended to evaluate persons or their work
- NOT an exam

Assessment of QMP - 1

- QMP - does it address all issues?
  - list of SOPs - Check though the list - Are all the required policies / procedures included?
  - look at a selection of SOPs and check...
    - Are the SOPs written according to the standards - e.g. do they include expected outcomes and tolerance limits?
    - Is there evidence of annual review and approval?
    - Is there evidence of good document control?
  - SOP manual
    - Is it available to all staff? - ask staff to find it
    - If its electronic, is there a hard copy? And do staff know how to access it? - ask them

Assessment of QMP - 2

- Assess if personnel follow SOPs
  - Observe a process and compare to written SOP (e.g. chemotherapy, infusion of stem cells)
  - Look for evidence that a specific element of a recent past procedure was carried out according to SOP (e.g. donor evaluation)
Assessment of QMP - 3

- **Training**
  - Is there documentation of training for medical staff, nursing staff, lab staff - ask to see departmental records, individual log books etc
  - Does this include regular safety training?
  - Is there documented competency for procedures staff regularly perform? Look at training records for specific SOPs

- **Deviations**
  - Is there evidence that deviations from SOPs are documented and approved? Ask quality officer or Processing facility director to show an example

Assessment of QMP - 4

- **Audit**
  - Is there a process and timetable for audit?
  - Is there evidence that there are regular audits? Ask for audit reports. Minutes of meetings
  - Is there evidence that the results of audits are disseminated to relevant staff?
  - Is there evidence that audit leads to improvements? Change of practice and re-audit?

- **Outcome Review**
  - Is there evidence of outcome review? Ask to see reports/minutes of meetings
  - Is engraftment data regularly monitored? Ask to see minutes of meetings

Assessment of QMP - 5

- **Adverse Events**
  - Is there a system for reporting?
  - Is the system used? - note number of reported AEs
  - Are they reviewed by PD?
  - Is a report available to patient's physician?
  - Is there evidence of corrective actions?
  - Ask to see reports/minutes of meetings

The Standards - Section B

- B 1. General - programme size and organisation
- B 2. Clinical Unit Facilities
- B 3. Personnel
- B 4. Quality management
- B 5. Policies and Procedures
- B 6. Donor selection, evaluation and management
- B 7. Therapy administration
- B 8. Clinical research
- B 9. Data management
- B 10. Records
Documentation - Clinical programme

- Submitted before inspection
  - Organigramme of programme
  - CVs, registration, evidence of training, educational activity for all senior medical staff
  - Nursing summary (staffing, training etc)
  - Quality manual and SOP for SOP
  - List of SOPs
  - Patient and donor consent forms
  - List of patients (Activity data)
  - MED-A data for 10 consecutive patients

- Documentation to see on site
  - Patient notes
  - Sample donor notes
  - Selected SOPs (e.g. donor evaluation)
  - Pro formas for HDT
  - Training records
  - Audit reports
  - Adverse Event (AE) reports
  - Minutes of meetings
  - Quality review meetings
  - Patient management meetings

Examples of Standards: Donor Evaluation Procedures for infectious disease

Within 30 days prior to (each) collection, each donor must be tested for evidence of infection by the following communicable disease agents:

- Human immunodeficiency virus, type 1
- Human immunodeficiency virus, type 2
- Hepatitis B virus
- Hepatitis C virus
- Human T-lymphotropic virus, type I*
- Human T-lymphotropic virus, type II*
- Treponema pallidum (syphilis)
- Cytomegalovirus - unless previously documented to be positive (not mandatory)

*HTLV will only be required if there are specific risk factors

B6. Donor Evaluation Procedures

Other tests

Allogeneic Donors

- HLA-A, B, DR typing by an EFI-accredited laboratory.
- ABO group and Rh type and appropriate red cell compatibility with the recipient.
- Pregnancy assessment for all female donors of childbearing potential *

* must be within 7 days of starting conditioning of allogeneic recipient or of starting mobilisation if autologous donor

Therapy Administration: How Inspectors Assess the Evidence

- Therapy administration
  - Ask to see protocols in the Unit and Pharmacy
  - Review patient charts to confirm treatment given
  - Interview pharmacist and nurses about normal practice
  - Ask nursing staff about chemotherapy training
  - May watch treatment being given to check practice against SOP
Recent Hot Topics for JACIE

- Early discharge from the transplant centre
- Air quality
- BM harvesting
- Programmes that move to new facilities (or update existing ones)
- Impact of the change to a 4 year accreditation cycle
- Extra-corporeal photopheresis/other ‘new’ therapies
- ICU Service provision
- Scope of the Standards

Early Discharge

- It is against the spirit of standards to inspect and accredit the centre performing the infusion as the “Transplant centre” without considering post-transplant care
- 4th edition
  - B2.4.5 “The Clinical Program shall ensure planned discharges are to facilities adequate for post-transplant care”
- Responsibility of the TC to ensure compliance with items such as - Isolation facilities
- Staffing and training
- Policies and procedures
- JACIE will require documentation of compliance and may include inspection of the hospital providing post-transplant care

Discharge - Period of Time Covered by Standards?

- Relevant standards B2.1-2.4
  - B2.1 There shall be a designated inpatient unit that minimizes airborne microbial contamination
  - B2.2 There shall be a designated area for outpatient care that reasonably protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation, and administration of intravenous fluids, medications, and/or blood products
  - B2.3.1 There shall be provisions for prompt evaluation and treatment by a transplant attending physician available on a 24-hour basis
  - B2.2.1 There shall be immediate access to an intensive care unit or equivalent coverage for critically ill patients

Clinical Units and Air Quality

- Relevant standards B2.1-2.4

Standards now recognise

- Variation in unit facilities - number, case mix, prevalence of opportunistic infections
- Increased use of ambulatory approaches with frequent day case review
- Do not imply that all units must have LAF
- Important to provide data on effectiveness of approaches used

Impact of the 4 year cycle

Proposal - to change the wording of the standards to bring the requirements into line with the accreditation cycle - change the absolute total activity to 40 for apheresis and 4 for BM harvests over 4 years (JACIE has different wording to FACT)

C1.4 For renewal accreditation:

- C1.4.1 For apheresis collection facilities, a minimum of forty (40) cellular therapy products shall have been collected by apheresis within an accreditation cycle
- C1.4.2 For bone marrow collection facilities, a minimum of four (4) bone marrow collection procedures shall have been performed within an accreditation cycle.

Bone Marrow Harvesting

- May be forgotten if very few harvests
- Minimum is 1 in 12 months before initial accreditation and 4 per 4-yr re-accreditation cycle
- Full Part C checklist e.g. Licensed physicians, good facilities
- Incorporate into QM e.g.SOPs
- Staff competency and experience
- If numbers too small Part C checklist not required

New Facilities in an Accredited Centre

- The Centre must notify JACIE of any changes to facilities as soon as they are completed and in use
- Point within accreditation period when change occurs

- In the final 12 months of accreditation: no revisit required, centre will be re-inspected within one year. Evidence of the effective date of the move required
- In the first 36 months of accreditation: centre must demonstrate new facility is compliant with the relevant standards. The centre submits documentation (see next slide) to JACIE within 3 months of completion of the move. If at the end of 3 months following this notification all documentation has not been received, accreditation of the affected part of the programme may be suspended.
New Facilities in an Accredited Centre

Required documentation

- Short description of the changed or new facility and their impact on the working of the programme e.g. if paediatric patients are now also treated, changes in staffing, etc
- Evidence of validation of facility including environmental checks and monitoring. This includes patient areas e.g. installation and monitoring of HEPA filters, as well as laboratory facilities e.g. air quality in LAF cabinets
- Plan/map and organigramme of the new facility
- Revised Quality Management Plan or Manual demonstrating that the change in facilities has been reflected
- Disaster plan

Extracorporeal Photopheresis

Should ECP be covered as a cellular therapy procedure within the FACT-JACIE Standards and therefore within the scope of inspections?

Proposal

- If ECP is part of therapy for GVHD/other indications in BMT patients in a transplant unit undergoing JACIE inspection and is performed on a site that is included in a JACIE inspection, the following sections of the standards apply
  
  (i) If using a closed circuit
  C1 General
  C2 Collection Facility
  C3 Personnel
  C4 Quality Management
  C5 Policies and Procedures
  C6 Donor Evaluation and Management
  C8 Process Controls
  C11 Records
  
  (ii) Additionally, if using an open circuit
  C7 Labels – requirement for a partial label
  C9 Cellular Therapy Product Storage
  C10 Cellular Therapy Product Transportation and Shipping
  C12 Direct Distribution to Clinical Program
  
  (iii) If transferred to processing facility

4th Edition - Admission to Intensive Care

- B2.4.7 “there shall be immediate access to an ITU or equivalent coverage for critically ill patients”
- Covers both inpatient programmes and outpatient facilities
- Arrangements must be documented
- IP within the facility; OP not necessarily on-site

Intensive Care Unit Access

The impact of transferring patients to another facility that is not in the same hospital should be monitored and this data should be used to assess whether or not the clinical programme meets JACIE requirements

Additional information:

- A concise description of access to ICU is now requested among the pre-inspection documentation e.g. SOPs describing the process for accessing ICU services
- Inspectors will be instructed to meet with ICU staff if possible during the on-site inspection and/or for an intensivist to attend the opening meeting of the inspection
Intensive Care Unit Access

- An ICU on the same site represents the optimal standard of care and that any deviations from this will be carefully reviewed.
- Centres with on-site access should have a contingency for when the on-site unit is full or unavailable.
- 'Equivalent coverage' is the ability to provide multisystem support including assisted respiration on-site for patients who will then be transferred to another hospital (in or outside the same health care provider) for more 'formal' ICU management.
- Access to ICU in terms of response time and time-in-transit should be very carefully monitored and documentation of this should be available at inspection.

Scope of the JACIE Standards

- JACIE aim to expand Standards wherever appropriate e.g. to new CTP.
- Clinical Standards apply only to HPC (and DLI).
- Collection accreditation largely restricted to HPC and DLI.
- Processing Facilities may receive other products. Inspection must evaluate the impact of these on HPC processing.

4th Edition - Collection Facility Director

- C3.2.2 “there shall be a collection facility director who is an individual with a medical degree or a degree in a relevant science”
  - requirement for a PhD dropped
  - Allows more nurses to become collection facility directors
  - Emphasis also on postgraduate training and experience.

Areas of deficiencies

Expressed as % of total deficiencies. Based on analysis of 1732 deficiencies encountered in inspections.
**Minor v Significant Deficiencies**

- Difference between a minor deficiency and a significant deficiency is a matter of judgement
- **Minor deficiencies**
  - generally involve correction to existing SOPs or other documentation
- **Significant deficiencies - examples**
  - Inpatient isolation facilities inadequate
  - No continuous temperature monitoring of freezers
  - Inadequate quality management programme

**Clinical Programmes - Most Common and Important Deficiencies**

- B6 - Donors
- B6.3.2 - IDMs not tested within 30 days of collection
- B9 - Data management
- B4.10.4 - Corrective actions
- B2.6 - Outpatient area
- Discharge

**B6.000 Donors - Problems**

- Lack of written donor information e.g. collection procedures and risks of G-CSF, central lines
- Missing/inconsistent donor info e.g. travel, transfusion, immunisation histories
- Lack of clear selection criteria
- No clear ‘final authorisation’
- Not relaying donor info to collection facility
- No record in patient record of donor suitability e.g. HLA, CMV, ABO

**SOLUTIONS**

- Clear, comprehensive and unambiguous policies and procedures
- Checklists
- Final approval documents

**Testing for IDMs**

- B6.3.2 “Within 30 d prior to collection all HPC donors shall be tested for evidence of clinically relevant infection – HIV 1/2, HBV, HCV, HTLV 1/2*, syphilis
- B6.3 states that “there shall be donor evaluation procedures to protect the recipient from the risk of disease transmission from the donor”
- Deficiencies – medical history doesn’t include the correct questions
  - specific tests e.g. syphilis omitted
  - not repeated if SCT delayed
Corrective actions

- B4.10.4 – “corrective action shall be implemented as appropriate”
- Deficiencies recorded – lack of audit
  - audit not regular
  - critical endpoints not defined
  - not disseminated
- Adverse events and clinical incidents not reported/recorded; absence of corrective actions

Data Management

- B9.1 and B9.2 describe the requirement to collect all TED/MED-A data and audit this regularly
- At a minimum – patient outcomes, donor screening and testing and recipient 100d mortality
- Deficits – incomplete or incorrect forms, lack of engraftment data
  - clinical status at SCT not well recorded
  - lack of chemo prescription, date of administration not recorded

Interactions Between Facilities

- Links between facilities are important e.g.
  - Written requests for collection, or component issue
  - Provision of engraftment data to collection and processing facilities
  - Reporting of adverse events to other facilities, if appropriate
  - Service agreements or contracts with external facilities

Impact of a Quality Management System on Outcome after HSCT

- Data from 107,000 HSCT 1999-2007 in 421 European Teams
- Analysis of overall survival, relapse incidence, non-relapse mortality and relapse free survival
- Outcome correlated with era of transplant: 3 years prior to application, during application and after JACIE accreditation
- Analysis clustered by team, stratified for type of HSCT, disease, year of HSCT, conditioning, Gross National Income/capita and adjusted by EBMT score as a key risk factor

Gratwohl et al, EBMT, 2009
Impact of a Quality Management System on Outcome after HSCT

- Improvement in outcome of allogeneic HSCT from pre-accreditation compared to post-accreditation
- Improvement of overall survival peaked at 14% for patients with chronic leukemias who received an allogenic HSCT
- Improvement in overall and disease-free survival was also apparent for recipients of high-dose chemotherapy supported with autologous HSCT
- Improvement in survival is \( \geq \) than the consequences of what are now thought of as major innovations in the field of HSCT

Gratwohl et al, EBMT, 2009; Chabannon et al, 2010 in preparation

JACIE - Future Developments

- Enhance training for transplant centres, inspectors and quality managers
- Active collaboration with FACT – Standards (5th Edition), quality etc
- Increase inspection activity in Europe and elsewhere
- In depth analysis of deficiencies
- Investigate accreditation for non-haematopoietic stem cell usage e.g. cardiac, 'scope of the standards'

HTA: Recent Developments

Cord Blood Collection
- From July 2008, any person collecting cord blood must be licensed by HTA or where appropriate, there should be a Third Party Agreement (TPA) with an HTA-licensed establishment
- Those collecting cord blood must be appropriately trained to ensure the collection takes place safely, and that the sample is not contaminated and is safe to use

The UK Stem Cell Toolkit
- A single resource for those who wish to develop a programme of stem cell research and manufacture, ultimately leading to clinical application. The Tool Kit consolidates existing regulatory resources and helps to clarify where the remit of individual regulators begin and end
- Developed in collaboration with GTAC and MHRA

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Alphabetical Notes to Accompany this Map
Advanced Therapy Medicinal Products (ATMPs)

Medicinal products based on:
- Genes – gene therapy
- Cells – cell therapy
- Tissues – tissue engineering

Engineered or subjected to substantial manipulation (not cell separation, concentration, purification or cryopreservation); not intended for the same essential function in the recipient as in the donor

- MHRA is the UK Competent Authority for manufactured products/IMPs classed as medicinal by EMEA, but HTA licences the donation, procurement and testing

Advanced Therapy Medicinal Product - Regulation

- Evaluation by Committee for Advanced Therapies - product characteristics, packaging, labelling.
- Traceability
- Efficacy and adverse reactions
- Examples (i) Autologous marrow to derive MSC and chondrocytes for tracheal regeneration (ii) Tumour activated NK cells

Stem Cell Storage

- Up front consent required by HTA and JACIE
- Should cover – cell storage and usage, testing requirements, data storage, use for research, discard if not used
- Research – small anonymised aliquots for QA testing, ethically approved research
Stem Cell Storage

- **Discard** – approval depends on whether the patient is still alive; conditions relating to cells and storage and patient/donor traceability

- **Duration of storage** – may be indefinite if techniques and storage conditions optimal (Rowley, 2005); studies showing that engraftment equal if <1-2 v 2-8 years of storage (Pawson et al., unpublished, Rowley, 2005)

Thank you for your attention