Introduction to FACT Immune Effector Cellular Therapy Standards and Accreditation

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Presentation Outline

• General information about Immune Effector Cell (IEC) Standards and accreditation
• Program characteristics
• Applying the Standards
What are Immune Effector Cells?

- Broadly defined as “cells that have differentiated into a form capable of modulating or effecting a specific immune response”

- Common products
  - Chimeric Antigen Receptors (CAR)
  - Therapeutic vaccines

- Donor lymphocyte infusion (DLI)
  - Not under the scope of IEC Standards and accreditation
  - Infusion is therapy; T Cells, Apheresis (or Whole Blood) is the product
  - Still managed in the accreditation process as they historically have been

- T cells
- B cells
- Natural Killer cells
- Dendritic cells
- Mesenchymal Stromal cells
Why Standards for Immune Effector Cells?

<table>
<thead>
<tr>
<th>FACT-accredited transplant programs</th>
<th>Drug manufacturers</th>
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<tr>
<td>• Participation in immune effector cell trials</td>
<td>• Investment in controlled, safe clinical trials</td>
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<td>• Desire to apply FACT requirements to these new services</td>
<td>• Ensure continued proper handling and use of products after licensure</td>
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<td>• Non-transplant units using immune-effector cells</td>
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**Patient Safety, Outcomes, and Access**

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<tr>
<th>Regulators</th>
<th>Payers</th>
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<tr>
<td>• Responsibility for approving only safe and effective products for licensure</td>
<td>• Anticipation of drug licensure → requests for reimbursement</td>
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<td>• Interest in field’s ability to handle toxicities</td>
<td>• Expectation of good outcomes for covered services</td>
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Why Accreditation for Immune Effector Cells?

- Different types of immune effector cells in different clinical situations are being used outside of, or in conjunction with, traditional transplant setting
- Some newer products associated with unusual, unexpected, and severe adverse reactions
- Lack of clarity concerning the meaning of accreditation
FACT Immune Effector Cell Task Force

<table>
<thead>
<tr>
<th>Helen Heslop, MD – Chair (ASGCT representative)</th>
<th>Marcela Maus, MD, PhD (SITC representative)</th>
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<tbody>
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FACT Common Standards as Starting Point: Task Force Conclusions

- Two purposes for Common Standards:
  - Encourage quality programs for cellular therapies not ready for standardized processes.
  - Serve as a starting point for new, specialized Standards

- Task force review of Common Standards:
  - Common Standards as published are generic and applicable to immune effector cells.
  - Some Standards – common and unique to immune effector cells – could be delineated.
  - Focus on clinical requirements (most unique).
  - Specific standards apply to immune effector cells regardless of the clinical setting in which they are administered.
  - Standards should be packaged in a format easily accessible to users regardless of clinical care structure.
Organization of the Immune Effector Cells: Accommodating Different Models of Care

- Common Standards
  - Immune Effector Cell Standards
  - Hematopoietic Cell Therapy Standards

Clinical departments separate from transplant (e.g., leukemia service) → Common Standards → Immune Effector Cell Standards

Transplant programs
Publications

FACT Common Standards for Cellular Therapies, First Edition
- Standards common to any type of cellular therapy
- Requirements within included in other sets of Standards
- Associated accreditation applies to programs not performing hematopoietic cell transplantation or immune effector cell therapy

FACT Standards for Immune Effector Cells, First Edition
- Common Standards + Immune Effector Cell-Specific Standards
- Apply to programs only performing immune effector cell therapy

FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, Edition 6.1
- HCT Standards + Immune Effector Cell-Specific Standards
- Apply to transplant units that may or may not administer immune effector cells

Scope of Immune Effector Cell Standards

• Processes – not science
  • Donor selection and management, collection, preparation for administration, administration of cells, management of adverse events, and evaluation of clinical outcomes
  • Quality Management (QM) program that establishes, maintains, monitors, and implements improvements
  • Manufacturing as it occurs under IND or equivalent in accredited laboratories
  • Education
Program Characteristics
Eligibility for Accreditation

• Blood and marrow transplant (BMT) clinical sites
  • Involvement of BMT physicians = Clinical Program assumes some or all responsibility for IEC therapy = mandatory
  • No BMT physician involvement = “renting out space” and sharing nursing resources = optional, shared or separate accreditation

• Non-transplant clinical sites
  • Examples include leukemia or lymphoma services

• Immunotherapy divisions or “institutes”
  • IEC therapy administered across several different clinical sites under the direction of same leadership
Incorporating IECs Into Existing Program

- Standards apply to every program
  - Integrate fully into existing QM program and Standard Operating Procedures; do not reinvent the wheel
  - Make IEC processes a routine part of the program; will not always be new to the program

- IEC products are becoming more common
  - If a program begins using these products, it must be in compliance with the Standards as part of starting the new activity

- What if a program does not use immune effector cells?
  - Immune effector cell-specific standards will not apply
  - Indicated by choosing “N/A” on Compliance Application
Relationships Among Different Clinical Units

• Some institutions will have both a transplant program and a separate clinical unit (e.g., leukemia or solid tumor service) that administer immune effector cells

• The units may choose to pursue separate accreditation

• The units may choose to share accreditation if:
  • Shared leadership
  • Shared quality management program
  • Shared staff training programs
Number of Trials, Products, and Recipients

- BMT Transplant Programs
  - Must meet minimum number of recipients as outlined in HCT Standards
  - Eligible for IEC therapy accreditation if a trial is open at the program or the program uses licensed products
  - Number of trials, enrolled recipients, and treated recipients vary widely
    - This has impact on inspection day as described later in presentation

- Stand-alone Program (i.e., no transplant services)
  - A minimum of five new patients required to *complete* accreditation, but programs can begin the accreditation process at any time
Collection Facilities

• Collection processes must meet the collection requirements in the Standards.
  • True for all types of products collected in a FACT-accredited collection facility.
  • This includes hematopoietic progenitor cells (HPCs), IECs, or any other type of cell collected.

• If utilizing a collection service that is not currently FACT-accredited, it must still be inspected for compliance.
  • Exception: products manufactured by a commercial pharmaceutical company.
Processing Facilities

• **FACT-accredited laboratories** manufacturing immune effector cells will be required to be accredited for more than minimal manipulation with next renewal.

• If an accredited transplant program administers immune effector cells manufactured by a **GMP laboratory** not related to the usual, **FACT-accredited facility**:
  • Clinical standards still apply
  • GMP laboratory may be eligible for accreditation under the FACT Common Standards for Cellular Therapies or solely under Part D of the Immune Effector Cell Standards (depending on scope of activities)
  • If not accredited, take steps to ensure the laboratory meets the FACT processing standards
  • Accreditation requirements will be phased in with the renewal cycle of the Clinical Program
Applying the Standards
Standards Specific to Immune Effector Cells

• Most requirements are common to any cellular therapy; also applicable to HPC transplant

• This segment will cover those that highlight unique aspects of administration and toxicities:
  • Third-party manufacturers
  • Cytokine release syndrome and other adverse events
  • Coordination and education among different departments
  • Data management
The Role of Clinical Trial Documentation in Compliance with FACT Requirements

- IND (US)
- Or
- HREC + CTN / CTX (Aus) Requirements

- FACT Standards

- QM Program Accessible Procedures Training

- Safety
- Outcome data
- Event reporting
- Protocol compliance

Science and Trial Design
Examples of Connecting Clinical Trial Documentation with FACT Standards

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<thead>
<tr>
<th>IND or equivalent Requirement</th>
<th>Challenge(s) related to Standards Compliance</th>
<th>Solution(s)</th>
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| Protocol compliance           | • Lack of specific details for staff performance  
                                 • Inaccessible, lengthy, or unknown | • Make job-specific SOPs that will enable compliance with protocols  
                                 • Reference protocol in SOPs, conduct protocol training |
| Outcome analysis              | • Outcomes already reported to IND holder  
                                 • Many different types of cells | • Forward outcome reports to QM program  
                                 • Group data by cell type if possible |

Confidentiality of an IND can still be protected by stating who can access the protocol directly, limiting who should follow what procedure(s), etc. Generally speaking, though, procedures for patient care required by the Standards do not require the use of proprietary information. Compliance with contracts with study sponsors is necessary.
Third-Party Manufacturers - 1

• The level of participation of the clinical service in manufacturing an immune effector cell product varies
• Regardless of where the product is collected or manufactured, responsibilities must be clearly defined
• Programs should have documentation of the quality of the manufacturing laboratory through:
  • A quality audit or report of a quality audit performed by the holder of the Investigational New Drug (IND) application
  • Certificate of Accreditation
  • Licensure
Third-Party Manufacturers - 2

• If cellular therapy products are received directly by the Clinical Program from a third-party manufacturer, the following responsibilities shall be defined at a minimum:
  • **Chain of custody** of cellular therapy products
    • From donor at collection, through transport/shipping, to recipient at clinical center
    • Clinical program must be confident this is the product intended for this recipient
  • Cellular therapy **product storage**
  • Verification of cellular therapy **product identity**
  • Management of **adverse events**
Cytokine Release Syndrome

• Definition: A reaction from the release of cytokines from cells targeted by an antibody or immune effector cells

• Pharmacies shall have access to *formularies adequate* to treat cytokine release syndrome and other expected complications of immune effector cell administration

• Physician, Advance Practice Provider/Professional, and Nurse *training and competency* must include care interventions to manage complications including:
  • Cytokine release syndrome
  • Cardiac dysfunction
  • Respiratory distress
  • Neurologic toxicity
  • Renal and hepatic failure
  • Disseminated intravascular coagulation
  • Anaphylaxis

• Procedures shall include detection and management of immune effector cellular therapy complications, including cytokine release syndrome and central nervous system disease
Cytokine Release Syndrome – 2

• There shall be a **regular assessment** of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction
  
  • There shall be a process for **rapid escalation** of care, increased intensity of monitoring, and relevant workup to address complications
  
  • **Communication** to, as relevant, clinical staff, intensive care units, emergency departments, and pharmacies shall be timely
  
  • The Clinical Program shall have **written guidelines** for management of complications, including the use of cytokine-blocking agents and corticosteroid administration

• Example situation to assess: how would a program manage delayed cytokine release syndrome after the hospital pharmacy closes?

• Potential sources of information during inspections: document reviews, record reviews, personnel interviews, role playing
Outcome Analysis and Data Management

• Review **outcome analysis and product efficacy** for immune effector cells using an endpoint of clinical function as approved by the Clinical Program Director
  • Endpoints often dictated by protocols
  • Has Clinical Program Director reviewed these? Has a review committee of some sort at the program reviewed them?

• **Should** collect all data elements included in the applicable **CIBMTR Cellular Therapy forms**
  • Define staff responsible for collecting data and, as appropriate, reporting data to institutional repositories and CIBMTR (reporting is **NOT** required)

• Audit:
  • Accuracy of clinical data on a periodic basis
  • Safety endpoints and immune effector cellular therapy toxicity management annually
Example Endpoints for Outcome Analyses

• Overall and treatment-related morbidity and mortality at 30 days, 100 days, and 1 year post transplant (required)
• Safety
• Time to white cell and platelet recovery
• Incidence of cytokine release syndrome and neurotoxicity
• Karnofsky performance status
• Target disease response
• Disease-free survival
Assessing Programs with Few or No Recipients

• Some requirements can be met no matter the number of recipients (examples: SOPs; training of physicians, nurses, pharmacists, and others; availability of medications)

• Mechanisms for other requirements must be implemented, but may not be completed depending on stage and size of trials
  • Outcome analysis, audits, trending of deviations and adverse events
  • Must provide documentation that demonstrates ability to compile information for future analysis: infrastructure in place that defines who will perform what processes when, and how
  • Update of progress made/analyses conducted at time of annual report

• Inspectors must note on the report:
  • Whether procedures have been written and approved (including forms, worksheets, etc.)
  • Activities that have begun but are not complete
## Challenges Related to Data for Outcome Analysis and Audits

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<tr>
<th>Challenge</th>
<th>Small Number of Recipients</th>
<th>IND Requirements vs QM Program</th>
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<tbody>
<tr>
<td>Challenge</td>
<td>Not enough data for trending outcomes</td>
<td>Already reporting to IND holder</td>
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<tr>
<td>&gt; Solution</td>
<td>&gt; Minimally need mechanism for compiling information over time</td>
<td>&gt; Provide copies of reports to Quality Manager/incorporate in QM Program</td>
</tr>
<tr>
<td>Challenge</td>
<td>Few cases to audit</td>
<td>Different cell types, protocols, etc. in INDs</td>
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<tr>
<td>&gt; Solution</td>
<td>&gt; Include audit on schedule later in year</td>
<td>&gt; “Aggregate” data does not mean all data; acceptable to divide data into relevant categories</td>
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*If amount of data limits ability to perform analyses and audits, program must submit a progress report with a plan for implementing requirements over time, and provide an update within the next annual report.*
Current FACT IEC Accreditation Numbers

• 28 HCT programs have been inspected for Immune Effector Cellular Therapy with their Hematopoietic Cellular Therapy inspection

• 3 HCT programs have been accredited for Immune Effector Cellular Therapy with their Hematopoietic Cellular Therapy program
Online Resources

• FAQs for Inspecting Immune Effector Cells
• Immune Effector Cell webpage
  • Publications referencing FACT
  • Educational recordings
• Standards and Accreditation Manuals
  • Free download
  • Print copies for purchase
Thank You