Introducing the FACT Standards for Immune Effector Cells

Sarah Nikiforow, MD, PhD
Presentation Outline

• Why Standards were developed
• Who edited the first draft and how
• Scope of the Standards
• Standards for immune effector cells
• Publication and updates
• Accreditation program
Why Standards for Immune Effector Cells?

- **FACT-accredited transplant programs**
  - Participation in immune effector cell trials
  - Desire to apply FACT requirements to these new services

- **Drug manufacturers**
  - Investment in controlled, safe clinical trials
  - Need for continued assurance of proper handling and use of products after licensure

- **Regulators**
  - Responsibility for approving only safe and effective products for licensure
  - Interest in field’s ability to handle toxicities

- **Payers**
  - Anticipation of drug licensure → requests for reimbursement
  - Expectation of good outcomes for covered services
# The FACT Immune Effector Cell Task Force

<table>
<thead>
<tr>
<th>Chair/Chair Designation</th>
<th>Chair/Chair Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helen Heslop, MD – Chair (ASGCT representative)</td>
<td>Marcela Maus, MD, PhD (SITC representative)</td>
</tr>
<tr>
<td>Baylor College of Medicine • Houston, TX</td>
<td>Dana Farber/Harvard Cancer Center • Boston, MA</td>
</tr>
<tr>
<td>Michael Lill, MD – Vice-Chair</td>
<td>Philip McCarthy, MD</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center • Los Angeles, CA</td>
<td>Roswell Park Cancer Institute • Buffalo, NY</td>
</tr>
<tr>
<td>Elizabeth Shpall, MD – Vice-Chair</td>
<td>Sarah Nikiforow, MD, PhD</td>
</tr>
<tr>
<td>MD Anderson Cancer Center • Houston, TX</td>
<td>Dana Farber Cancer Institute • Boston, MA</td>
</tr>
<tr>
<td>Carlos Bachier, MD</td>
<td>Jae Park, MD</td>
</tr>
<tr>
<td>Sarah Cannon BMT Program • Nashville, TN</td>
<td>Memorial Sloan-Kettering Cancer Center • New York, NY</td>
</tr>
<tr>
<td>Kevin Curran, MD</td>
<td>David Porter, MD</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center • New York, NY</td>
<td>Penn Medicine • Philadelphia, PA</td>
</tr>
<tr>
<td>David Maloney, MD, PhD</td>
<td>Phyllis Warkentin, MD</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center • Seattle, WA</td>
<td>University of Nebraska &amp; FACT CMO • Omaha, NE</td>
</tr>
</tbody>
</table>
Scope of Immune Effector Cell Standards

- Cells used to **modulate an immune response** for therapeutic intent
  - May elicit a response or mitigate a response
  - Cell types **include dendritic, natural killer, T, and B** (does not include MSCs)

- Common products
  - Chimeric antigen receptor T cells (**CAR-T cells**)
  - Therapeutic vaccines using dendritic cells

- 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
  - Education
FACT Common Standards as the Starting Point

• Two uses:
  • Encourage quality programs for cellular therapies not ready for standardized processes
  • **Serve** as a starting point for new, specialized Standards

• Review of Common Standards:
  • Focus on clinical requirements (most needed)
  • Verify Common Standards were appropriate
  • Add requirements specific to immune effector cells
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)

Transplant programs
Organization of Standards: How they Relate

- Immune Effector Cell Standards
- Hematopoietic Cell Therapy Standards
- Common Standards
Resulting Set of FACT Standards

FACT Common Standards for Cellular Therapies
- Standards
- Guidance under development

FACT-JACIE Hematopoietic Cell Therapy Standards
- Standards
- Accreditation Manual

NetCord-FACT Cord Blood Banking Standards
- Standards
- Accreditation Manual

FACT Immune Effector Cell Standards (draft)
- Standards
- Accreditation Manual
Interim Standards for Transplant Programs

• Transplant programs utilizing immune effector cells will be expected to be in compliance with new standards once effective
  • Clinical unit
  • Collection facilities if collection is performed at program
  • Processing facilities as relevant to activities performed:
    • Manufacturing the product in house
    • Receiving the product from third-party manufacturer and preparing it for administration

• Accredited programs already have mechanisms to establish compliance
  • QM program, document control system, etc.
  • Create new or update existing processes to include immune effector cells
What if we do not use immune effector cells?

- Immune cell-specific standards will not apply
- Indicated by choosing “N/A” on Compliance Application
- However, these products are becoming more commonly used
  - If your program begins using these products, be in compliance with the standards as part of starting the new activity
- Donor lymphocytes for infusion (DLI) are already included in the FACT-JACIE Standards and can be handled as they are currently managed
Requirements for Immune Effector Cells

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

• This presentation 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

• Some new requirements should be applied to everything you do, even if not immune effector cells
  • Example: cytokine release syndrome for haploidentical transplants
Third-Party Manufacturers

- The level of participation in manufacturing an immune effector cell product varies
- Regardless of where the product comes from, 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
Third-Party Manufacturers

• 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
  • 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

- 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
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

• Review overall and treatment-related mortality at 30 days in addition to 100 days and 1 year after administration

• 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 data elements** included in **CIBMTR Cellular Therapy forms** on a periodic basis
  • Safety endpoints and immune effector cellular therapy toxicity management annually
Eligibility for Accreditation

• FACT-accredited transplant programs administering immune effector cells must comply with the new requirements and be inspected under them.

• Clinical departments not associated with a transplant program may submit an application, which will be reviewed by the FACT Board of Directors.

• A minimum of five new patients required to complete accreditation, but programs can begin the accreditation process at any time. Manufacturers will be made aware of this “chicken before the egg” issue.
Inspection Under Interim Standards

- **FACT-accredited programs** will need to report whether they use immune effector cells at their next annual report or renewal application.

- Compliance is expected and will be verified during the next routine on-site inspection.
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 administers 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
Relationship with Different Laboratory

• If an accredited transplant program administers immune effector cells manufactured by a GMP laboratory at its institution but 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
  • The GMP laboratory must begin process of becoming compliant with FACT Standards and pursuing accreditation
Thank You