Introducing the FACT Standards for Immune Effector Cells

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AT THE UNIVERSITY OF NEBRASKA MEDICAL CENTER

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

Patient Safety, Outcomes, and Access

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

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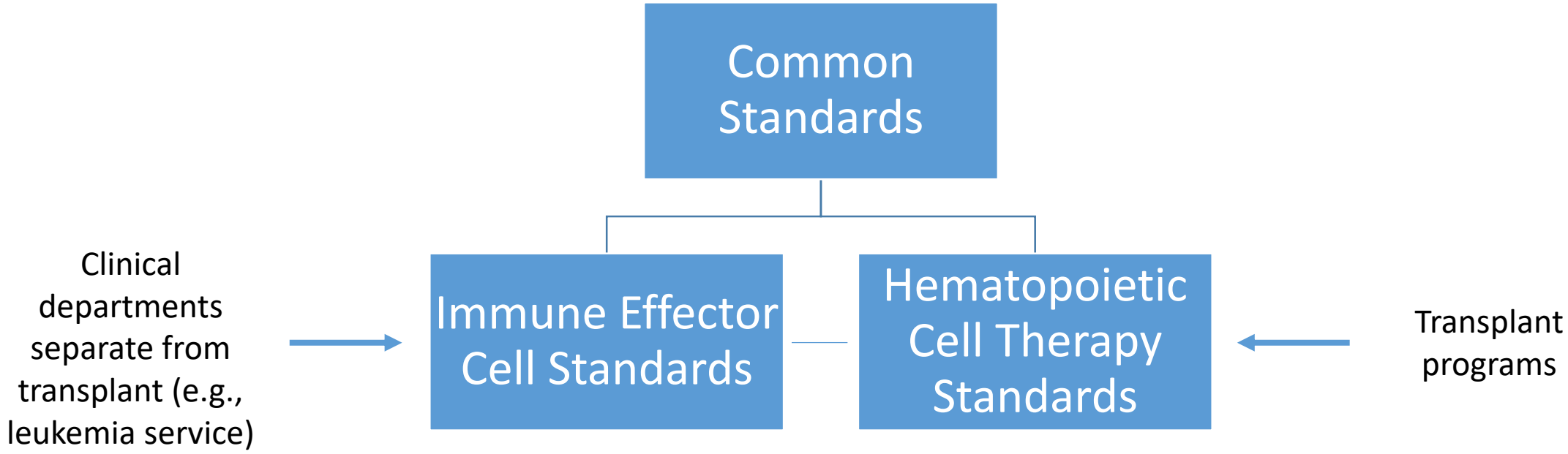
Scope of Immune Effector Cell Standards

- 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

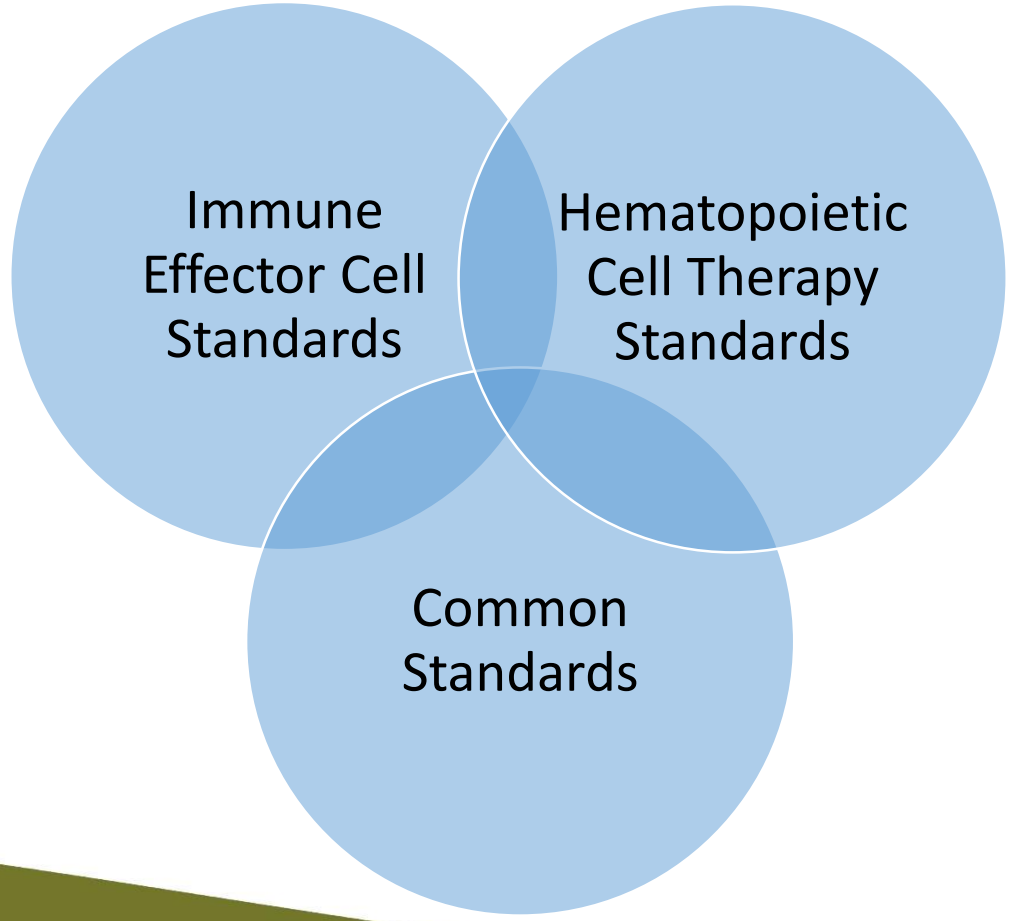
FACT Common Standards as the Starting Point

- 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



Organization of Standards: How they Relate



Resulting Set of FACT Standards

FACT Common Standards for Cellular Therapies	FACT-JACIE Hematopoietic Cell Therapy Standards	NetCord-FACT Cord Blood Banking Standards	FACT Immune Effector Cell Standards (draft)
Standards	Standards	Standards	Standards
Guidance under development	Accreditation Manual	Accreditation Manual	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