June 15, 2018

Tamara Syrek Jensen
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: National Coverage Analysis for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers

Dear Ms. Syrek Jensen:

The Foundation for the Accreditation of Cellular Therapy (FACT) appreciates the opportunity to submit comments regarding the National Coverage Analysis (NCA) for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers. We support Medicare coverage of CAR T-cell therapies, and we believe local coverage policies are better suited for flexible updates in this rapidly evolving field as new data become available. The purpose of this letter is to provide information regarding how FACT standards and accreditation promote the safety and effectiveness of these therapies.

The mission of FACT is to improve the quality of cellular therapy through peer-developed standards, education, and accreditation for the benefit of patients. As the non-profit standards and accreditation arm of the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy (ISCT), FACT is founded on the idea that collaboration and advice from peers drive continuous improvement. Professionals expert in their respective fields who hold themselves to a higher standard are in the best position to maintain quality, safety, controlled delivery of therapies, and appropriate data. These all protect an environment of patient safety and access.

History of FACT Accreditation

Since 1996, FACT has been a leader in improving the quality of cellular therapy processes in the fields of hematopoietic progenitor cell (HPC) transplantation and cord blood banking through its program of professional standards and voluntary accreditation. FACT Standards are developed by consensus of experts active in the field, based on published evidence whenever possible. Drafts are published for peer and public review and comment before finalization (including review of each edition by the Food and Drug Administration [FDA]). Voluntary accreditation is based on submitted documents and an on-site inspection conducted by experts active in the field and qualified by requisite training and experience.

FACT first set Standards[i] and administered an accreditation program in HPC transplantation. Based on its established standards-setting and accreditation program, payers began requiring FACT accreditation as a criterion for reimbursement and designation of centers of excellence. Some clinical trial groups, such as the Bone Marrow Transplant Clinical Trials Network (BMT CTN) and Children's Oncology Group (COG), require FACT accreditation for participation. The trust and recognition of stakeholders in FACT

University of Nebraska Medical Center • 986065 Nebraska Medical Center • Omaha, Nebraska 68198-6065, USA
Tel: (402) 559-1950 • Fax: (402) 559-1951

accreditation led to subsequent requests for Standards and accreditation for cord blood banking[ii], emerging cellular therapies[iii], and, most recently, immune effector cells[iv].

FACT Standards and Accreditation for Immune Effector Cellular Therapy

In 2017, FACT published the *FACT Standards for Immune Effector Cells* and implemented an accompanying accreditation program. An immune effector cell is defined by FACT as, "a cell that has differentiated into a form capable of modulating or effecting a specific immune response." This definition includes CAR T-cell therapies. The Standards and accreditation program were created in response to interest from several stakeholders, including drug manufacturers and immune effector cell clinical programs. Regulators and payers have also used FACT accreditation as an indication of quality.

The Standards require a comprehensive quality management program, provider training in the specific therapies administered, defined and written protocols, adverse event management, and evaluation and reporting of safety endpoints and clinical outcomes, preferably via the Center for International Blood and Marrow Transplant Research (CIBMTR). The Standards are applicable to immune effector cell therapies wherever they are administered, and have already contributed to the safety and quality of clinical trials, regulatory approval, and reimbursement, thereby increasing patient access to these lifesaving cells. CAR T-cell therapies have inherent differences from traditional pharmaceuticals. Cellular therapies consist of live cells that require special handling to retain viability and potency, exist in lot sizes of one for a specific patient and therefore require considerably robust chain of custody processes, and remain in the patient for an extended half-life. CAR T-cell therapies also present significant toxicities in a large percentage of patients.[v,vi] FACT-accredited immune effector cell programs will be educated, trained, and well equipped to safely administer and manage these therapies.

Programmatic Risks Related to Immune Effector Cellular Therapy

FACT Standards and accreditation do not outline requirements for the scientific validity of CAR T-cell therapies; rather, they expect a robust quality and safety program in which the therapies are administered. At the time of this letter, FACT has accredited 31 immune effector cellular therapy programs, and has conducted or scheduled 25 additional inspections. All but one of the accredited programs is part of an HPC transplant program. The most common citations, and a brief case study for each, are listed below:

- Development of an infrastructure to accommodate these types of cellular therapies
    - A program performed outcome analysis of CAR T-cell therapies only within the context of Investigational New Drug (IND) records, rather than in aggregate as part of the quality management program. The program implemented an outcome analysis process that defines the clinical endpoint for this therapy, requires providers to assess patients for this endpoint at defined time points, and incorporates those results into a comprehensive analysis.

- Quality management issues, including audits, adverse events, and staff training
    - Adverse event management for a program was only described in a CAR T-cell-specific document that was not widely accessible to nursing staff. To address this deficiency, the program revised its nursing orientation and training checklists to include training modules for immune effector cells, cytokine release syndrome, and neurologic toxicity. Nurses are now required to complete tests related to the content in these training modules. The program also updated its procedures to outline steps to take in the case of adverse events, and implemented these changes in its online procedure management system.
- Establishment of policies and standard operating procedures
    - A program did not have written guidelines for the use of cytokine-blocking agents and corticosteroid administration. This is important not only for managing adverse events, but also for maintaining the efficacy of the treatment. Prior to receiving FACT accreditation, the program submitted guidelines as part of its procedure for immune effector cell administration.
- Data management and reporting
    - Immune effector cell-related data were not reported by a program to an institutional repository or to CIBMTR. The program is required to define staff responsible for this task and the data registry to which the information is reported prior to receiving FACT accreditation.
- Defining responsibilities with third-party manufacturers, including chain of custody and labeling
    - A program received a CAR T-cell product for which the identification of the patient was unclear. The program outlined steps to take when this occurs, including contact with the product's manufacturer.

Due to the reported toxicities of CAR T-cell products, the products currently approved by the FDA are administered under Risk Evaluation and Mitigation Strategies (REMS). These strategies include provider education, preparative regimens, adverse event management, and discharge instructions. While these REMS play an important role in patient safety, they are specific to the product itself and do not comprehensively address programmatic requirements for administering cellular therapies. FACT Standards provide a framework for developing a quality program and mitigate the risks of provider and staff errors due to disparate and voluminous product-specific requirements.

FACT welcomes the opportunity to discuss productive alignments we may be able to offer CMS as it assesses the appropriateness of providing coverage of CAR T-cell therapies. We encourage CMS to consider how the *FACT Standards for Immune Effector Cells* and its accompanying accreditation program may assist CMS and clinical units, collection facilities, and cell processing laboratories with promoting quality and safe administration of these therapies.

Thank you for considering these comments. We hope you find them useful. If you have any questions, please do not hesitate to contact us.

Sincerely,

Dennis Gastineau, MD
President, FACT
Director, Human Cellular Therapy Laboratory
Mayo Clinic
Ph: 507-284-8737
Email: gastineau.dennis@mayo.edu

Helen Heslop, MD
Chair, FACT Immune Effector Cell Task Force
Professor of Medicine and Pediatrics
Baylor College of Medicine
Ph: 832-824-4662
Email: heheslop@txch.org

Phyllis I. Warkentin, MD
Chief Medical Officer, FACT
Medical Director, Biologics Production Facility
University of Nebraska Medical Center
Ph: 402-559-6871
Email: pwarkent@unmc.edu

---

[i] Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee – ISCT and EBMT. (2018). *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* (Seventh Edition). Available: factwebsite.org

[ii] Foundation for the Accreditation of Cellular Therapy and International NetCord Foundation. (2016). *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration* (Sixth Edition). Available: factwebsite.org

[iii] Foundation for the Accreditation of Cellular Therapy. (2015). *FACT Common Standards for Cellular Therapies* (First Edition). Available: factwebsite.org

[iv] Foundation for the Accreditation of Cellular Therapy. (2018). *FACT Standards for Immune Effector Cells* (First Edition, Version 1.1). Available: factwebsite.org

[v] Novartis. (2018). Kymriah™ *Full Prescribing Information.* Available: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf

[vi] Kite, a Gilead Company. (2017). Yescarta™ *Full Prescribing Information*. Available: https://www.yescarta.com/files/yescarta-pi.pdf