



March 15, 2019

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

Re: Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

Dear Ms. Syrek Jensen:

The Foundation for the Accreditation of Cellular Therapy (FACT) appreciates the opportunity to submit comments regarding the Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N). This letter provides a brief overview of FACT and our comments on the proposed decision memo.

Brief Overview of FACT

The mission of FACT is to improve the quality of cellular therapy through peer-developed standards, education, and accreditation for the benefit of patients. It is the non-profit standards and accreditation arm of the American Society for Transplantation and Cellular Therapy (ASTCT, recently renamed from the American Society for Blood and Marrow Transplantation) and the International Society for Cell and Gene Therapy (ISCT). Some payers require FACT accreditation as a criterion for reimbursement and designation of centers of excellence, and some clinical trial groups require FACT accreditation for participation.

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In 2017, FACT published standards and implemented an accompanying accreditation program for immune effector cells (IECs), which includes CAR T-cell therapies. FACT Standards and accreditation require a robust quality and safety program in which the therapies are administered. The Standards and accreditation program were created in response to interest from several stakeholders, including drug manufacturers and IEC clinical programs. Regulators and payers have also used FACT accreditation as an indication of quality. FACT-accredited IEC programs are educated, trained, and well equipped to safely administer and manage these therapies.

At the time of this letter, FACT has accredited 183 hematopoietic progenitor cell (HPC) transplant programs, and 58 of these programs are also accredited for IECs. An additional program is accredited as a stand-alone IEC program. FACT has also conducted or scheduled 21 inspections of other transplant programs seeking IEC accreditation.

For additional details regarding FACT's history and its standards and accreditation program for IECs, see our comments submitted in regards to the National Coverage Analysis for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers dated June 15, 2018.

Comments Regarding Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

1. Decision Summary, A: *“The Centers for Medicare & Medicaid Services (CMS) proposes to cover autologous treatment with T-cells expressing at least one chimeric antigen receptor (CAR) through coverage with evidence development (CED) when prescribed by the treating oncologist, performed in a hospital, and all of the following requirements are met:*
 1. *Patient has:*
 - a. *Relapsed or refractory cancer; and*
 - b. *not currently been experiencing any comorbidity that would otherwise preclude patient benefit.”*

We agree that the CMS should cover CAR T-cell therapies for its beneficiaries, and that the therapies should be administered in hospitals meeting the guidelines described within the proposed decision memo.

Congruent with the position of ASTCT, we are concerned that a National Coverage Decision (NCD) with CED increases barriers to access to this lifesaving therapy. We also encourage CMS to cover CAR T-cell therapies approved by the Food and Drug Administration (FDA) in accordance with the product label. There are currently clinical trials underway to study CAR T-cells in different contexts, such as first-line therapy or from an allogeneic donor, and

more can be expected. The specification of autologous therapy for relapsed or refractory cancer may cause the NCD to become outdated. Finally, we encourage CMS to clarify that the physician treating a patient determines if the risks of any comorbidities outweigh the potential benefits of CAR T-cell therapy.

2. Decision Summary, A.2: *“The hospital has: a. a Cellular Therapy Program consisting of an integrated medical team that includes a Clinical Program Director, a Quality Manager, and at least one physician experienced in cellular therapy, and demonstrates that protocols, procedures, quality management, and clinical outcomes are consistent from regular interaction among all team members; b. a designated care area that protects the patient from transmission of infectious agents and allows for appropriate patient isolation as necessary for evaluation and treatment; and c. written guidelines when administering CAR T-cell therapy for patient communication, monitoring, and transfer to an intensive care unit.”*

We agree with the inclusion of hospital requirements that are congruent with FACT Standards for the medical team’s leadership, experience, integration, care areas, and guidelines. These requirements will promote patient safety and CAR T-cell efficacy.

3. Decision Summary, A.3 and A.4.c:
 - *“ . . . then the patient must be enrolled in, and the furnishing hospital is participating in, a prospective, national, audited registry that consecutively enrolls patients, accepts all manufactured products, follows the patient for at least two years, adheres to the standards of scientific integrity and relevance to the Medicare population as identified in section A.4 of this decision, and answers the three following CED questions:”*
 - *“The study results are not anticipated to unjustifiably duplicate existing knowledge.”*

We have some questions related to data collection and reporting, and would appreciate clarification regarding potential noncoverage if patients do not consent to collection and reporting of their health-care related data, or if they become lost to follow-up or refuse additional data collection despite hospitals’ good-faith efforts.

We support the use of the Center for International Blood and Marrow Transplant Research (CIBMTR) as a national registry to promote consistent data and reduce the reporting burden on providers. We suggest that the CIBMTR be included in decision documents and the National Coverage Determination (NCD) Manual as an example of an existing registry. The CIBMTR has experience with collecting data from providers, auditing data for accuracy, providing data back to the providers for analysis, and establishing risk-adjusted algorithms

for evaluating patient outcomes. It administers the Stem Cell Therapeutic Outcomes Database (SCTOD) for HPC transplantation and serves as the Cellular Immunotherapy Data Resource (CIDR) for the Immuno-Oncology Transplantation Network (IOTN). CIBMTR has the ability to provide its services to a wide variety of cellular and gene therapy manufacturers.

The CIBMTR is currently working with at least two CAR-T manufacturers to incorporate their requirements into data forms, and the manufacturers have indicated they will be using the CIBMTR for their registries. It has also developed an electronic Patient-Reported Outcomes collection system (ePRO). These initiatives allow efficient use of resources and a consistent source and format of data for evaluation.

Given providers' experience with CIBMTR, and CIBMTR's efforts to incorporate IECs (including CAR T-cells) into its databases, use of this organization's services will support the proposed decision memo's statement that study results do not unjustifiably duplicate existing knowledge.

We suggest that CMS begin certifying CIBMTR as a registry for purposes of CED to avoid a gap in coverage between when the decision memo is finalized and when the CIBMTR may be certified.

4. Decision Summary, A.3.a.ii and A.3.b.i and VIII. CMS Analysis, Outpatient Setting:

- *“and answers the four following CED questions: . . . How does the patient report their symptom function health-related quality of life changes over the course of their treatment?”*
- *“and submit to CMS for approval a written executable analysis plan to address all of the following CED questions: How does the patient report their symptom function and health-related quality of life changes over the course of their treatment?”*
- *“. . . Therefore, we are concerned about seriously ill patients with relapsed or refractory cancer who receive CAR T-cell therapy without a hospital inpatient admission to receive specialized care and monitor for serious AEs. To this end, consistent with NCCN guidelines, and the limited information regarding use of an FDA-approved product inconsistent with an FDA indication for use, we also propose that patients receiving CAR T-cell therapy for any other use and patients provided CAR T-cell therapy without hospital inpatient admission must address the CED question of how the patient feels their health-related quality of life changes over the course of their treatment and to this end collect patient's health-related quality of life . . .”*

- “. . . we also propose that patients receiving CAR T-cell therapy for any other use and patients provided CAR T-cell therapy without hospital inpatient admission must address the CED question of how the patient feels their health-related quality of life changes over the course of their treatment and to this end collect patient’s health-related quality of life using an NIH patient-reported outcome assessment, including the PRO-CTCAE and PROMIS.”

We request more clarification on the utility of quality of life data. The proposed decision only requires such reporting after outpatient administration or administration under specific National Comprehensive Cancer Network (NCCN) guidelines. As described in the memo, this is due to concerns related to caregivers’ and support networks’ abilities to recognize and handle adverse events. This is a valid concern that we agree should be addressed; however, additional clarity regarding the required timeframes for submitting quality of life data is requested. The proposed decision requires data to answer the CED questions at 3 months, 6 months, 12 months, and 24 months. Given the proposed decision memo’s explanation for requiring patient-reported outcomes, and the typical onset of adverse events following CAR T-cell administration, it is unclear why quality of life data at six months and beyond are necessary. Obtaining data this frequently from patients may be difficult to achieve and may not address the concern of adverse event management.

In regards to tools used to report quality of life, we suggest the use of the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®). This system collects data more applicable to quality of life measures; the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) focuses more on safety. Furthermore, the CIBMTR is incorporating (PROMIS®) into its ePRO system, and use of this tool would promote consistency and harmonization.

Similar to our suggestion to certify CIBMTR as a registry prior to finalization of the proposed decision memo, we suggest that quality of life data not be required until a patient-reported outcomes (PRO) protocol is approved and operational. CIBMTR has a data collection protocol that is already approved by programs’ Institutional Review Boards (IRBs), is operational, and collects data to answer the other CED questions; however, this activity does not currently include PRO collection. CIBMTR already has infrastructure for PRO collection, but drafting of a protocol and approval of IRBs will be required.

5. Decision Summary, A.3.a.iii: *“The furnishing hospital shall address the CED questions on all registry patients by tracking the following clinical data elements at baseline, at treatment,*

and at follow-up 3 months, 6 months, 12 months, and 24 months after the treatment is administered.”

If CED data are required, we agree that hospitals furnishing the CAR T-cells should submit follow-up data. Follow-up will not likely be a major priority of primary oncologists, and we believe that reporting should be analogous to HPC transplantation in which a data coordinator obtains data. We suggest aligning required time points for data with existing CIBMTR protocols, FACT Standards, and other regulatory agencies to promote consistency in data and minimize burden to programs.

Long-term follow-up has been a challenging task in HPC transplantation, especially the posttransplantation period when patients return to health care providers not involved with the transplant. We expect similar challenges with CAR T-cell therapy and request clarification regarding potential retroactive loss in coverage if patient data cannot be obtained.

6. VII.B.6. Professional Society Recommendations / Consensus Statements / Other Expert Opinion: *“Foundation for the Accreditation of Cellular Therapy (FACT). Standards for Immune Effector Cell Administration. First edition, version 1.1. March 2018 . . . The objective of the Common Standards is stated to promote quality medical and laboratory practice in cellular therapies as an emerging and evolving field . . .”*

We agree that inclusion of FACT Standards in the proposed decision, and expectations that practitioners and providers comply with them, is important for safe and efficacious administration of CAR T-cell therapies.

The proposed decision memo references the *FACT Standards for Immune Effector Cells*, but describes the *FACT Common Standards for Cellular Therapies*. There is no reference to the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*, which are currently the Standards most commonly applied to accredited IEC programs. FACT Standards are arranged to accommodate the various care delivery models employed by health care institutions so that accredited services are clearly delineated. The following paragraphs better clarify how the FACT Standards apply to IECs.

Most institutions administer IEC therapies, including CAR T-cells, within their HPC transplant programs. For these programs, the requirements are incorporated into the current edition of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*. All requirements in these Standards

apply to IECs as they are relevant (for example, IECs must be fully incorporated into the program's Quality Management program, personnel training programs, and process controls).

For clinical programs that do not perform HPC transplantation, the current edition of the *FACT Standards for Immune Effector Cells* applies. These Standards include only those requirements that apply to IEC therapies; transplant-specific requirements (for example, monitoring of engraftment) are not included. Future use of these Standards is expected to grow as institutions begin administering IECs outside of transplant programs; however, at the time of this letter, only one program is accredited under these Standards.

The *FACT Common Standards for Cellular Therapies* includes the basic fundamentals any type of cellular therapy program should employ, and is the basis of the other, more specific Standards. It is a separate document that does not include specific requirements for IECs.

For making coverage decisions for CAR T-cell therapies, we believe your decision documents and NCD Manual should reference 1) the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* and 2) the *FACT Standards for Immune Effector Cells*. The Standards are updated every three years, and we suggest that the "current edition" be referenced rather than specific editions. Information in the proposed decision memo regarding the Standards development process and requirements of clinical programs is correct for both of these sets of Standards.

7. Appendix A, Generalizability of Clinical Evidence to the Medicare Population: *"The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice."*

This section acknowledges the difference in quantity or type of attention given to trial participants in different medical settings, and questions the applicability of study findings to community-based practices. FACT Standards can be applied in any type of health care institution; however, they do require a robust infrastructure that would take time for inexperienced institutions to build. Given that provision of CAR T-cells within the commercial construct is new, we agree that such therapies should only be provided in accredited centers.

8. VIII. CMS Analysis, Practitioner and Provider Requirements: *“Standards we would expect to find in a Cellular Therapy Program are included in the Foundation for the Accreditation of Cellular Therapy (FACT) Common Standards for Cellular Therapies (2015) and Standards for Immune Effector Cell Administration (2016) and describe quality management guidelines to incorporate performance data, as well as policies and procedures that address risk management of operations . . . We believe adherence to criteria consistent with a nationally accredited Cellular Therapy Program promotes patient safety, and ensures best patient outcomes and optimal CAR T-cell therapy administration. We note that FACT accreditation, which considers these criteria, is also consistent with current practice by CAR T-cell manufacturers and participating hospitals involved with the administration of CAR T-cell therapy and care of patients.”*

We agree with your determination that CAR T-cell therapies should be administered in hospitals accredited under requirements that are included within the FACT Standards. As the memo states, these therapies have known toxicities that require experience, training, facilities, and procedures for mitigating, responding to, and evaluating adverse events. Additionally, our experience since implementing the IEC accreditation program has shown that implications of commercial access to these therapies, rather than within a research program, introduces additional challenges related to chain of custody, staff training, and data reporting. The FACT Standards and accreditation program requires and verifies processes to address these challenges.

In addition to CAR T-cell manufacturers’ requirements for FACT accreditation, payers have begun implementing or are considering FACT accreditation as a requirement for reimbursement or centers of excellence. Continued harmonization of this requirement will increase consistency and reduce burden across providing organizations. Stakeholders have expressed with FACT a desire for clarification whether FACT accreditation completely satisfies this requirement or if hospitals would be required to further confirm they meet coverage requirements via other requirements. We suggest that FACT accreditation of immune effector cellular therapy be sufficient.

We also believe this section should reference the current editions of the following FACT Standards: 1) the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* and 2) the *FACT Standards for Immune Effector Cells*.

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,



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