Data-Informed Optimization of CAR T-Cell Therapy Long-Term Follow-Up

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Short Title

Long-Term Follow-Up After CAR T-Cell Therapy

Abstract

Following administration of chimeric antigen receptor (CAR) T-cell therapy, extensive long-term follow-up (LTFU) requirements and complex data collection processes have posed significant challenges for patients and providers. To reassess whether a 15-year LTFU period remains scientifically justified, we convened a multistakeholder working group that included representatives from patient advocacy groups, academia, industry, and government. This analysis incorporates newly aggregated primary data on composite percentages of adverse events reported by year for five FDA-approved CAR T-cell therapies. Combined with previously published research, the findings indicate that adverse events are infrequently reported after five years post-infusion, and that adverse events of primary concern—based on the mechanism of action of CAR T-cell therapy—predominantly occur within the first five years. Based on these data, we recommend reducing the LTFU data collection requirements to five years in both clinical trial and commercial settings. Additionally, we propose a streamlined process that leverages technological advancements to automate the transfer of focused safety data from electronic health records (EHRs) into a third-party database. To facilitate implementation, we recommend feasibility testing of this updated data collection approach using an established platform. We also outline regulatory policy considerations to most effectively enable adoption of these recommendations.

Keywords: Chimeric Antigen Receptor T-Cell Therapy; Long-Term Follow-Up; Adverse Events; Electronic Health Records; Real-World Data; Regulatory Policy

Introduction

When the first chimeric antigen receptor (CAR) T-cell therapy was approved by the Food and Drug Administration (FDA) in 2017,[i] long-term safety sequelae were unknown. Since then, more than 30,000 patients have been treated with CAR T-cell therapy, and seven CAR T-cell therapies have been approved. The totality of data over 14 years since cancer CAR T clinical trials began supports a positive benefit/risk profile and, in some cases, the curative potential of CAR T-cell therapy. This positive CAR T-cell therapy experience to date coupled with the current technology-enabled environment requires a re-examination of the current long-term follow-up (LTFU) process and regulatory requirements to ensure they remain both scientifically justified, and patient centered. In this paper we argue that the accumulated data support

shortening and streamlining the LTFU requirements, and we provide recommendations on how to do so.

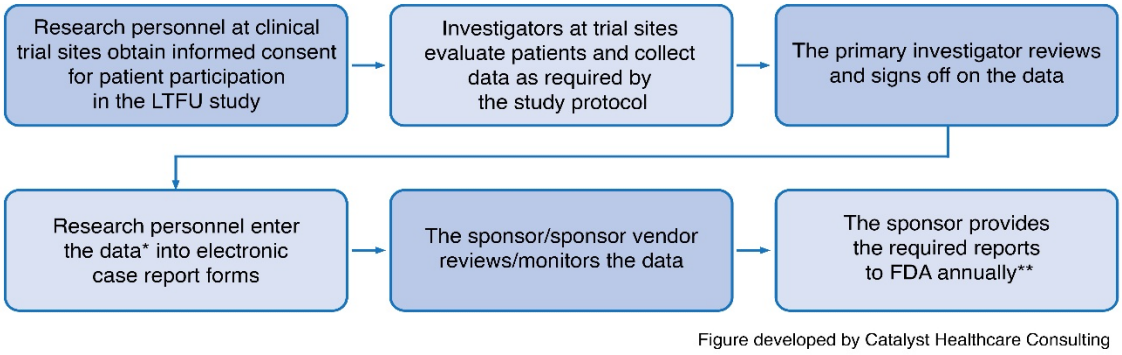
Current LTFU data collection requirements and process

CAR T-cell therapies, which currently use integrating viral vectors to introduce the CAR gene into T cells, have a theoretical risk of insertional oncogenesis. Due to a concern that patients treated with CAR T-cell therapy may develop second primary malignancies (SPMs), or new cancers that are independent of an original malignancy, the FDA to date has required 15 years of LTFU data collection for all participants receiving CAR T-cell therapies in clinical trials and for a significant subset of patients receiving the CAR T-cell products in the commercial setting. More recently, the FDA stated in November 2023 that patients and clinical trial participants receiving CAR T-cell therapy products should be monitored for new malignancies for life.[ii] As further detailed below, the current LTFU data collection requirements and process are extensive and complex.

Clinical study administration

For participants receiving CAR T-cell therapy products in clinical trials, FDA guidance[iii] indicates the investigator should prepare and maintain adequate and accurate case histories on each participant, which should include information from scheduled visits. Physical examinations with a healthcare provider are recommended for the first five years after infusion, and investigators are recommended to contact participants at a minimum of once a year for the full 15-year duration. Investigators are to report LTFU data to the study sponsor, who in turn reports data to the FDA (Figure 1).

Figure 1. Typical process for collecting LTFU data from clinical trial participants



*Data typically include adverse events (AEs) or serious AEs; health status information from a physical examination, answers to questionnaires, telephone or email communications; and information on targeted concomitant medications, subsequent therapy, survival status and, for pediatric studies, growth, development, and sexual maturity status. The persistence of modified/CAR T cells is monitored at least annually until vector sequences become undetectable.
**Sponsors also provide reports to FDA when expedited reporting of qualified events is required or in response to requests for information.

Commercial CAR T-cell product administration

In the commercial setting, safety monitoring is fulfilled via post-marketing requirements (PMRs). To date all approved CAR T-cell therapies have PMRs that require study of significant numbers of patients for 15 years—up to 1500 patients for initial product approvals and between 300 and 1500 additional patients for new indications of a product (Table 1).

Table 1. FDA post-market requirements for FDA-approved CAR T-cell therapies

Approval date	Product Generic name (Brand Name)	Indication	Number of patients in post-approval safety study
11/8/24	Obecabtagene autoleucel (Aucatzyl)	B-cell precursor acute lymphoblastic leukemia	500
5/30/24	Lisocabtagene maraleucel (Breyanzi)	Mantle cell lymphoma	PMR for new indication:300
5/15/24	Lisocabtagene maraleucel (Breyanzi)	Follicular lymphoma	PMR for new indication: 300
4/5/24	Ciltacabtagene autoleucel (Carvykti)	Multiple myeloma, second line	PMR for earlier line of therapy: 200
4/04/24	Idecabtagene vicleucel (Abecma)	Multiple myeloma, third line	PMR for earlier line of therapy: 200
3/14/24	Lisocabtagene maraleucel (Breyanzi)	Small lymphocytic & chronic lymphocytic leukemia	PMR for new indication: 300
6/24/22	Lisocabtagene maraleucel (Breyanzi)	Large B-cell lymphoma, second line	PMR for earlier line of therapy: 0
5/27/22	Tisagenlecleucel (Kymriah)	Follicular lymphoma	PMR for new indication: 300
4/01/22	Axicabtagene ciloleucel (Yescarta)	Large B-cell lymphoma, second line	PMR for earlier line of therapy: 0
2/28/22	Ciltacabtagene autoleucel (Carvykti)	Multiple myeloma, fifth line	1500
10/01/21	Brexucabtagene autoleucel (Tecartus)	Adult acute lymphoblastic leukemia	PMR for new indication: 500
3/26/21	Idecabtagene vicleucel (Abecma)	Multiple myeloma, fifth line	1500
3/05/21	Axicabtagene ciloleucel (Yescarta)	Follicular lymphoma	PMR for new indication: 300
2/5/21	Lisocabtagene maraleucel (Breyanzi)	Large B-cell lymphoma, third line	1500
7/24/20	Brexucabtagene autoleucel (Tecartus)	Mantle cell lymphoma	500
5/01/18	Tisagenlecleucel (Kymriah)	Diffuse large B-cell lymphoma	PMR for new indication:1500
10/18/17	Axicabtagene ciloleucel (Yescarta)	Large B-cell lymphoma, third line	1500
8/30/17	Tisagenlecleucel (Kymriah)	B-cell precursor acute lymphoblastic leukemia, patients up to 25 years of age	1000

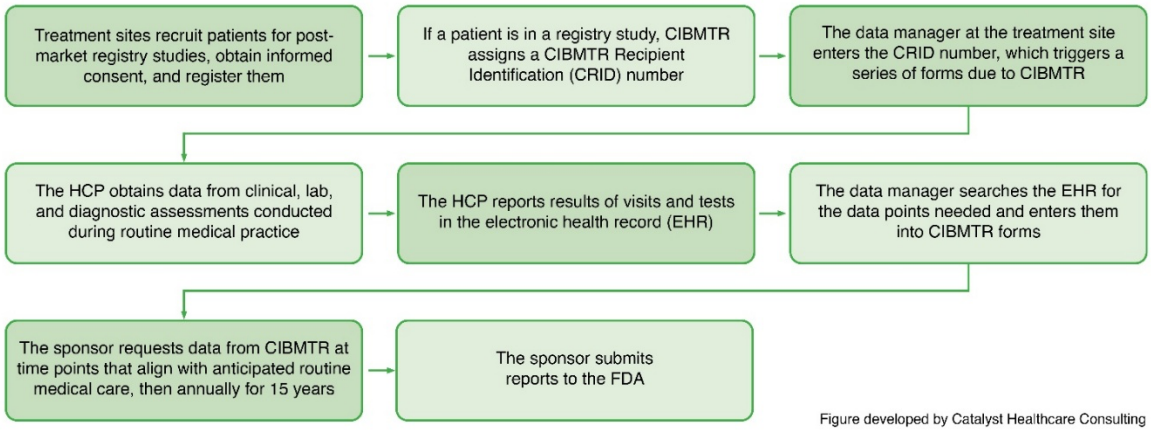
Products receiving approval for earlier lines of therapy have typically required either no additional PMRs or a small number of additional patients (i.e., 200) to be studied.

Sources: Catalyst Healthcare Consulting and FDA supporting documents, including Summary Basis for Regulatory Actions, Approval Letters, and Clinical Review Memos

For patients receiving commercial CAR T-cell therapy products within a post-approval safety study (PASS), the process for collecting LTFU data is similarly extensive and complex. Treatment sites typically report follow-up data to a patient registry, with the primary patient registry run by the Center for International Blood and Marrow Transplant Research (CIBMTR). Per the LTFU guidance document, the FDA may recommend use of a patient registry as the mechanism for data collection.[iii]

Data managers at treatment sites must manually locate data in a patient's electronic health record (EHR) and enter that data into a series of up to approximately 14 CIBMTR forms, each of which contains between seven and 522 questions. While a few of the forms are specific to certain types of cancer or certain subsequent occurrences after infusion (e.g., secondary malignancy, pregnancy), many of the forms need to be completed for all CAR T-cell therapy recipients, ranging from one time for some forms (e.g., pre-infusion baseline data) to every follow-up visit (e.g., post-cellular therapy follow-up at day 100, six months, one year and annually thereafter). Figure 2 provides an overview of the typical process for collecting post-market registry study data.

Figure 2. Typical process for collecting LTFU data for patients treated with commercial products



The safety data reported to the FDA include the development of subsequent neoplasms, cause of death for patient deaths, and the incidence and severity of cytokine release syndrome (CRS), neurologic toxicities, serious infections, prolonged cytopenias, hypogammaglobulinemia, and pregnancy outcomes in females of childbearing potential.

Challenges of the current LTFU data collection requirements and process

The length and complexity of the current LTFU process place significant burdens on patients and providers.

Patient burden and loss to follow-up

A recent Emily Whitehead Foundation and Catalyst Healthcare Consulting study[iv] of nearly 100 CAR T-cell therapy recipients observed significant patient attrition over the follow-up period. Notably, 20% of CAR T-cell therapy recipients who received their infusion more than a year ago had stopped going to follow-up visits. Moreover, of respondents who were treated recently (within a year), more than a third (38%) did not see themselves following up for 15 years, most of whom did not see themselves following up for more than eight years.

The top challenges identified in attending follow-up visits per the survey were travel-related, including distance to the treatment site and travel costs. Over half of respondents (53%) indicated that they lived more than two hours away from their original treatment site, with nearly a third (31%) living more than six hours away.

Provider/investigator burden: Duration and cost

In both trial and commercial settings, the LTFU process involves multiple steps and is resource intensive for providers and investigators (Figures 1 and 2).

In investigator-sponsored trials, the investigator/sponsor typically does not receive research funding to cover the costs of LTFU data collection and needs to identify alternative funding sources. Academic medical centers must hire additional staff to perform the manual collection and entry of long-term safety data. In the commercial setting, typical staff requirements are approximately one data manager/coordinator for every 60 – 65 commercial CAR T-cell therapy recipients.[1] These staffing costs far exceed the amount of compensation the

[1]Providers interviewed for this paper employ up to six full-time equivalent data managers/coordinators.

providers receive from the registry.[2] Furthermore, if patients choose to receive follow-up care with a community oncologist closer to where they live, academic medical centers may lack the resources needed to continue to report data to CIBMTR.

In recent years, there has been growing momentum to administer CAR T-cell therapy in community settings, with the goal of increasing patient access to what may be a life-saving treatment.[v] Community-based oncologists are unlikely to have the financial resources to obtain data managers, nor do they have the time needed to complete the extensive forms in addition to providing patient care. Thus, there is heightened urgency to promote streamlined approaches to data collection as CAR T moves into the community setting.

Solutions to address challenges

Reassess duration of follow-up based on evidence

Our analyses show that AEs in general tend to be reported within the first three years and rarely after five years; the vast majority of SPMs occur within the first five years,[vi,vii,viii] and T-cell malignancies in particular tend to occur within the first two years after infusion[ix]. Moreover, no causal association via insertional oncogenesis between CAR T-cell therapy and SPMs, including T-cell malignancies, has been demonstrated.[x,xi,xii] These findings are further elucidated below.

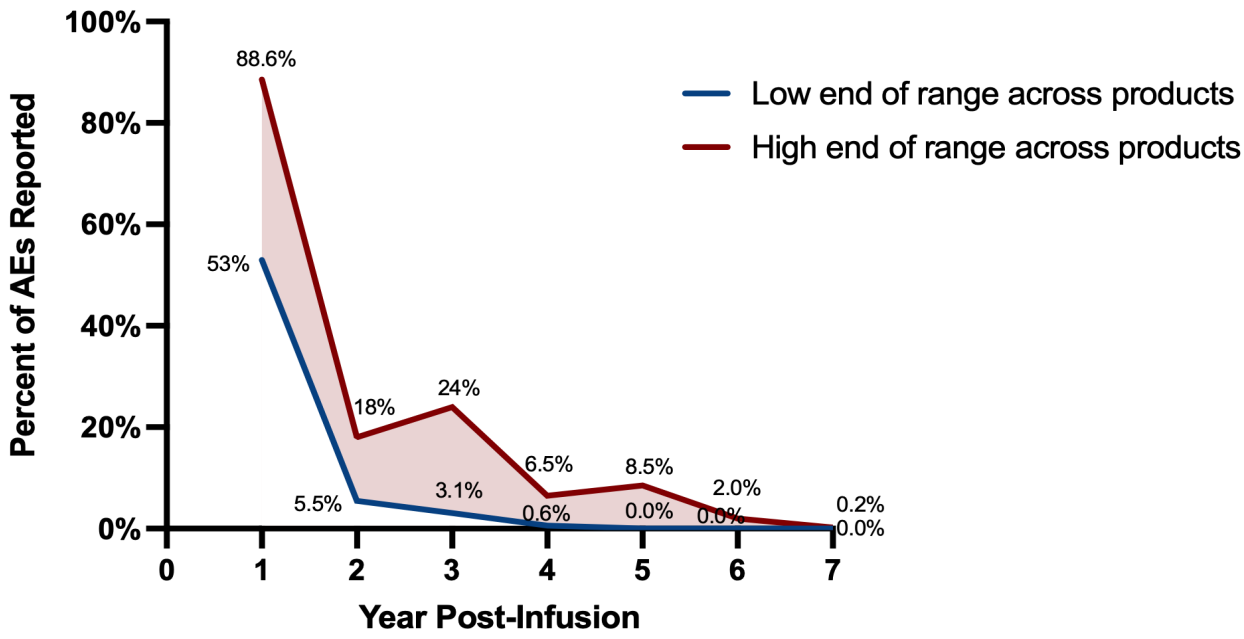
Long-term safety reporting is more robust within the context of a clinical trial, wherein follow-up periods and assessments are mandated for sponsors and AEs are solicited, than AE data collected within the post-marketing setting. For this paper, developers of five FDA-approved CAR Ts have interrogated their global safety databases to assess the reporting ratios of AEs within their pivotal clinical trials and long-term follow-up protocols (Figure 3).[3] With median follow-up times of 24–64 months, the majority (53%–88.6%) of AEs were reported in the first year after infusion (Figure 3). A drop in the percentage of the total reported AEs was observed after the first year—5.5%–18% in year two; 3.1%–24% in year three; 0.6%–6.5% in year four; and 0% – 8.5% in year five. After year five, event reporting reached or approached

[2]CIBMTR in turn receives funding from a variety of sources, including National Institutes of Health (NIH) awards, United States (US) Office of Naval Research grants, industry sponsors, the National Marrow Donor Program (a nonprofit organization), and the Medical College of Wisconsin.

[3]Detailed methods are available in the supplemental materials.

zero (0%–2% reported in year six and 0%–0.2% in year seven). Please note this data may be limited in interpretability due to potential differences in data collection and reporting into the global safety databases among sponsors, notable differences in duration of follow-up, patient attrition over time (lost to follow-up, death, consent withdrawn), and the evolving nature of global safety database reporting. This analysis reflects all AEs over this time period.

Figure 3. Range of percentages of total adverse events (AEs) reported in each year across five CAR T products



Since chemotherapy and/or radiation therapy can cause SPMs, we reviewed the literature for SPM development after CAR T-cell therapy relative to SPM development after standard of care (SOC) therapy. Across reports that had up to six years of follow-up, the frequency of SPMs after CAR T--cell therapy (0.4%–6.2%)[vi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx] was similar to the frequency of SPMs after receiving SOC treatments (4%–7%)(Table 2).[xiii,xiv,xv,xxi]

Table 2. Frequency of SPMs after CAR T vs. standard of care*

Study	After CAR-T			After standard of care (SOC) for blood cancers		
	Frequency of SPMs	**Number of patients in study**	**Median follow-up time (months)**	**Frequency of SPMs**	**Number of patients in study**	**Median follow-up time (months)**
Abramson, et al., 2023[xiii]	**3%**	89	17.5	**7%**	91	17.5
Rodriguez-Otero, et al., 2023[xv]	**6%**	225	18.6	**4%**	126	18.6
San-Miguel, et al., 2023[xiv]	**4.3%**	208	15.9	**6.7%**	211	15.9
Jadlowsky et al., 2025[vi]	**2.3%**	783	18.7			
John, et al., 2025[xix]	**0.4%**	703	28			
Ghilardi et al., 2024[xvi]	**3.6%**	449	10.3			
Hamilton et al. 2024[xii]	**3.5%**	724	15[1]			
Thieblemont, et al., 2024[xviii]	**6.2%**	97	53			
Tix, et al., 2024[xxii]	**6%**	5,517	21.7			
Pasquini, et al., 2020[xvii]	**2.4%**	255[2]	13.4			
Laetsch, et al., 2023[xx]	**1.3%**	79	38.8			
Miret, et al., 2023[xxi]				**6%**	7,807	21.2[4]
Sahebi, et al., 2018[xxiii]				**5.3%**	3,204[3]	72[5]

*The majority of studies reported frequencies rather than incidence rates, with the exceptions noted below. Median follow-up times should be considered when interpreting these results, and studies cannot be directly compared given heterogeneities across studies.

[1] Excluding non-melanoma skin cancers

[2] Children and young adults

[3] After autologous hematopoietic stem cell therapy

[4] Represents mean follow-up vs. median follow-up
[5] Represents cumulative incidence at 72 months after infusion vs. median follow-up

Although the overall frequency is low, hematological malignancies (i.e., myelodysplastic syndrome, acute myeloid leukemia, T-cell lymphoma) have been reported to occur at a slightly higher frequency after CAR T-cell therapy (0.8%–2.2%),[xii,xiv,xv,xvi,xvii,xviii,xxii,] than after SOC treatments (0%–1.4%)(Table 3).[xiv,xv,xxiii,xxiv]

Table 3. Frequency of hematologic malignancies after CAR T vs. standard of care*

Study	After CAR-T			After standard of care (SOC)		
	Frequency of hematological SPMs	**Number of patients in study**	**Median follow-up time (months)**	**Frequency of hematological SPMs**	**Number of patients in study**	**Median follow-up time (months)**
Rodriguez-Otero, et al., 2023[xv]	**1%**	225	18.6	**0%**	126	18.6
San-Miguel, et al.,2023[xiv]	**1.4%**	208	15.9	**0%**	211	15.9
Ghilardi et al., 2024[xvi]	**1.1%**	449	10.3			
Hamilton, et al., 2024[xii]	**1.9%**[1]	724	15			
Thieblemont, et al., 2024[xviii]	**2.1%**	97	53			
Tix, et al., 2024[xxii]	**2.2%**	5,517	21.7			
Pasquini, et al., 2020[xvii]	**.8%**	255[2]	13.4			
Laetsch, et al., 2023[xx]	**1.3%**	79	38.8			
Joelsson, et al., 2022[xxiv]				**0.7%**	32,100	85
Sahebi, et al., 2018[xxiii]				**1.4%**	3,204[3]	72[4]

*The majority of studies reported frequencies rather than incidence rates, with the exceptions noted below. Median follow-up times should be considered when interpreting these results, and studies cannot be directly compared given heterogeneities across studies.
[1] In addition to this frequency, this study found a 6.5% cumulative incidence at 3 years post-infusion
[2] Children and young adults
[3] After autologous hematopoietic stem cell therapy
[4] Represents cumulative incidence at 72 months after infusion vs. median follow-up

The higher frequency of hematological malignancies observed in patients treated with CAR T-cell therapy relative to SOC treatments is likely attributable to patient factors rather than

the CAR T-cell therapy itself.[xxv,xxvi] The relapsed/refractory population who is eligible for CAR T-cell therapy is typically older and has received multiple rounds of chemotherapy (e.g., an average of 10 cycles for patients with non-Hodgkin lymphoma). In a retrospective analysis of 511 patients with non-Hodgkin lymphoma who were treated with CAR T-cell therapy between September 2017 and August 2023, Gazeau and colleagues reported that patient age and number of prior therapies—but not CAR T-cell therapy—were statistically significant risk factors for the development of treatment-related myeloid neoplasms (e.g., acute myeloid leukemia and myelodysplastic syndromes).[xxv] In another recent report, Farina and colleagues reported that most patients who developed secondary myeloid malignancies following CAR-T cell therapy exhibited high-risk mutations (del7 and TP53).[xxvi] Genetic alterations were seen in some patients prior to therapy, suggesting an additional adverse prognostic factor for SPM development.[xi]

Due to the mechanism of action of CAR T-cell therapy, which involves integration of the CAR gene into the T cell's genome, T-cell malignancies are the SPM of primary concern. Significantly, FDA leaders concluded last year that T-cell malignancies after CAR T-cell therapy have been rare.[ix] The FDA reported that as of the end of 2023, it had become aware of 22 cases of T-cell malignancies after treatment with five of the six therapies approved at the time, but that the small sample size and variation in CAR T-cell product precluded conclusions about a possible association. Importantly, FDA leaders stated:

"With more than 27,000 doses of the six approved products having been administered in the United States, the overall rate of T-cell cancers among people receiving CAR T-cell therapies appears to be quite low, even if all reported cases are assumed to be related to treatment."[ix]

Other studies have reported rare cases of T-cell malignancies after CAR T-cell therapy,[xxvii] with frequencies also well below 1% (0.09%–0.5%).[vi,xii,xiv,xvi,xxii] No cases of second T-cell malignancy have been reported in several studies.[xviii,xix,xx,xxviii,xxix]

In the FDA report, three cases of T-cell malignancies for which genetic sequencing had been performed showed the presence of the CAR transgene.[ix] However, the presence of neoplastic CAR positive T cells does not itself prove that the CAR is responsible for the malignancy.[x] and a causal role for CAR T cells in the development of T-cell malignancy has yet to be demonstrated.[xi,xii]

When new malignancies occur after CAR T-cell therapy, they tend to occur relatively early. A 2025 study[vi] of 783 participants receiving T-cell therapy in clinical trials for cancer or HIV-1 infection found that the vast majority of new malignancies occurred within five years of infusion, except a single case of papillary thyroid cancer that occurred at year 14. In another study of 420 patients receiving CD19 CAR T-cell therapy, the median time to diagnosis of a second malignant neoplasm was 3.2 years (range, 0.6 – 8.2 years), leading to a five-year cumulative incidence of subsequent malignant neoplasms of 1.5%.[vii] According to CIBMTR data on 11,345 recipients of commercial CAR T as of February 2024, the median time from CAR T-cell infusion to the first subsequent neoplasm was 9 months.[viii] In the FDA report, the 14 cases of T-cell malignancies with adequate data occurred within two years (range, 1–19 months) of CAR T administration.[ix]

The theoretical risk for SPMs was the initial catalyst for lengthy follow-up of products with integrating viral vectors. Since CAR T-cell therapy has not been shown to cause SPMs and the vast majority of SPMs occur within the first five years of CAR T-cell infusion, we are recommending a decrease in the duration of LTFU data collection to five years.

Modernizing the process: Technological tools and standards for data collection

EHR interoperability, or the ability of different EHR systems to communicate and exchange patient information, is central to modernizing the LTFU process. Technology and data standardization have improved EHR interoperability, and the advances are already being translated into practice. The largest EHR vendor, Epic Systems Corporation,[xxx] has a longstanding health information exchange (HIE) platform, Care Everywhere, that has enabled EHR interoperability since 2008.

More recently, in 2022, the Assistant Secretary for Technology Policy's Office of the National Coordinator for Health Information Technology (ASTP/ONC) completed the establishment of the Trusted Exchange Framework and Common Agreement (TEFCA), which is a nationwide framework for health information sharing. As of 2023, more than 60% of hospitals indicated that they planned to participate in TEFCA.[xxxi] Recent standardization of clinical study data from real-world data sources has also furthered interoperability (i.e., the Fast Healthcare

Interoperability Resources technical standard[xxxii] and the US Core Data for Interoperability standardized data elements).[xxxiii]

Third-party platforms have started to leverage EHR interoperability to enable direct data exchange. For example, the Data Transformation Initiative (DTI) of CIBMTR is able to provide direct data exchange from a transplant center to the registry for certain fields following hematopoietic cell transplantation.[xxxiv] Using the CIBMTR Reporting App, available in the Epic App Market, data managers can push a button to transmit data directly from the EHR to CIBMTR, where the data is ingested into the CIBMTR Outcomes Database.

The most pertinent example of this capability is FDA's Biologics Effectiveness and Safety (BEST) Initiative. In 2017, the FDA Center for Biologics Evaluation and Research (CBER) launched the BEST Initiative to enhance post-market AE reporting and serve as an active surveillance program for biologics. Through its Innovative Methods (IM) Initiative, the BEST team developed a prototype of the Exchange Platform which uses automated detection of potential AEs from EHRs, using highly sensitive data elements, followed by semi-automated validation and reporting.[xxxv] To pilot the platform, the BEST IM team leveraged the nonprofit health information exchange network, eHealth Exchange, to query and receive data from the network partners. In 2023, CBER presented the results of one of its pilots, in which the platform was used to retrieve clinical data for post-vaccination AEs from 11 health provider partners using Epic EHRs.[xxxvi] The results indicated the overall data quality met general requirements for regulatory grade data quality, thereby successfully validating that an exchange platform is a feasible means to automate the exchange of AEs.

BEST protects patient privacy by having data providers retain control over their data, which remain behind data partners' local firewalls, and study results are returned to eHealth Exchange via a web portal in an aggregated format with all identifiers removed. When individual level information is required, all individual identifiers such as names, addresses, phone numbers, and other identifying data elements are removed before information is shared with the database.

The FDA indicates that artificial intelligence (AI) may also play a role in the identification, evaluation, and processing for reporting post-marketing adverse experience information.[xxxvii] Separate from the post-vaccination AE pilot, the BEST Initiative has utilized AI in other previous studies and continues to explore its use in current pilot studies.

We recommend a third-party platform, like the one used by the BEST pilot, to be used to transfer LTFU data points. A step toward this goal would be for CBER's BEST Initiative to prioritize a feasibility assessment of the use of an automated data exchange platform for CAR T-cell therapy specifically, or more broadly for a related gene therapy product class. Such a study could inform the operationalization of a platform to streamline the collection of post-market safety data for these products. In addition, we recommend that LTFU data collection be refined to focus on AEs that have more theoretical potential to be related to CAR T-cell therapy by using more precise AE definitions.

Recommendations

In summary, we are proposing the following recommendations:

1) **Shorten the LTFU requirement for CAR T-cell clinical trial studies and post-approval safety studies for marketed CAR T-cell products to 5 years**

For clinical trial participants, we recommend the FDA revise its guidance in the document, *Long Term Follow-Up After Administration of Human Gene Therapy Products,* to state that in general, the recommended duration of a LTFU protocol is 5 years for delayed AEs for CAR T-cell therapies using integrating vectors.

We also propose incorporating this 5-year LTFU recommendation into the draft guidance document that is due to be issued by September 30 of this year, per a PDUFA VII commitment—*Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on Cell and Gene Therapy Products*. Similarly, for post-approval safety studies for marketed CAR T-cell products (if required and as determined on an individual product basis), we recommend a 5-year duration for all delayed events, including SPMs. In addition, we encourage the FDA to consider decreasing the number of patients to be studied for PMRs because post-market product data can be supplemented by data from clinical trials. Continued passive monitoring through standard HCP spontaneous voluntary reporting of AEs to *MedWatch* could be recommended for both clinical trial participants and patients receiving a product in the commercial setting.

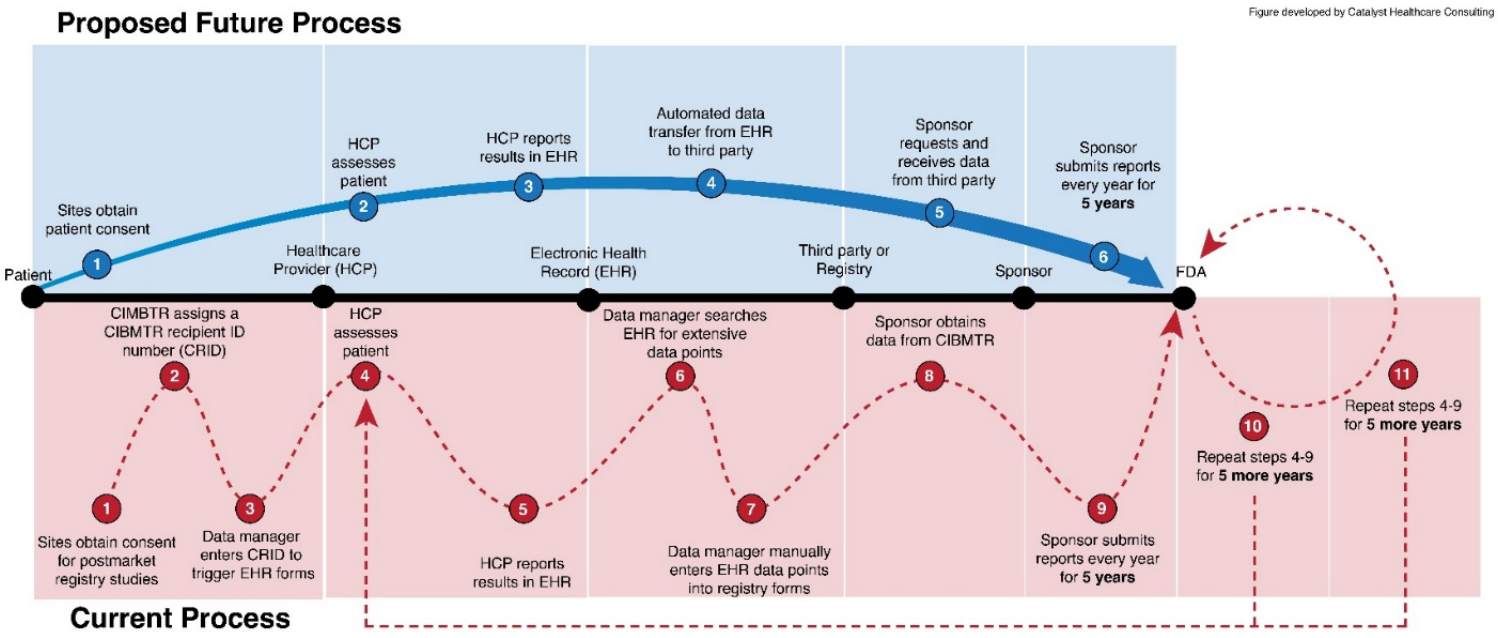
2) **Streamline the AE data collection process through the automated exchange of EHR data to a central third-party database**

We recommend the development of a platform, similar to that used in the BEST Initiative, to enable the automated secure transfer of patient and clinical trial participant data between HCPs and regulators. We suggest that CBER's BEST team continue their efforts with a feasibility assessment of the use of its automated data exchange platform for CAR T-cell therapy or a related gene therapy class.

Due to the challenges of the current manual process of data collection and entry into registries, we also propose that the FDA allow sponsors the flexibility to select their data collection mechanism. We recommend the FDA update the LTFU guidance document to delete the statement that the FDA "may recommend that [a sponsor] establish a registry or use an existing patient registry..." for data collection[iii]. We encourage the FDA to give sponsors the choice of data collection mechanism, such as the use of a third-party database and/or new technologies (like AI), to enable the development and use of less resource-intensive methods.

We show a proposal for a streamlined process in Figure 4.

Figure 4. Streamlining of collection of post-market safety data



3) Streamline AE data collection requirements

Currently, the long-term toxicities that need to be reported are within the following general categories: SPMs, new or exacerbated neurologic disorders and autoimmune disorders, new

hematologic disorders, and *any* AEs or conditions that may have a reasonable relationship with CAR T-cell therapy. The use of more precise AE definitions by the entity collecting data would better capture relevant safety information, while decreasing the reporting burden on stakeholders, by collecting only data on more precisely defined AEs. We propose definitions for the scope of AE collection for each AE category in Table 4. We recommend that data collection entities, in collaboration with other stakeholders, narrow the number of questions on data forms to reflect a more focused, relevant scope of AE data collection.

Table 4. Proposed scope of AE data collection

AE Reporting Categories	**Proposed scope of AE Data Collection**
Second primary malignancies	Newly diagnosed malignancy only; Recurrence or progression of an existing malignancy would not qualify
New or exacerbated neurologic disorders	New incidence or exacerbation of a pre-existing serious neurologic disorder and any condition requiring neurological consult and examination
New or exacerbated autoimmune disorders	New incidence or exacerbation of a pre-existing autoimmune disorder
New hematologic disorders	New incidence of serious hematologic disorder, including hypogammaglobulinemia, B-cell aplasia, and prolonged cytopenia
Other AEs or conditions that may have a reasonable relationship to therapy	For patients with disease progression and initiation of subsequent treatment, only serious infections considered possibly related by the treating physician need to be reported

Conclusion

In the 14 years since the first-in-class clinical trials began and with over 30,000 patients treated, CAR T-cell therapy has proven to be an effective life-saving treatment with curative potential and an established safety profile. For CAR T-cell-eligible patients with limited time, removing barriers to treatment access and easing treatment burden are of utmost criticality. The current 15-year LTFU requirement is not justified in light of the long-term safety data

summarized herein. Shortening and automating the LTFU requirements of CAR T-cell therapy would be a significant step forward in breaking down the barriers that currently impede access to this groundbreaking treatment.

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Declaration of Competing Interests

The authors declare the following financial interests and personal relationships that may be considered potential competing interests:

- Betsy Foss-Campbell, MA – serves as a consultant for Kite Pharma.
- Nancy Myers, JD – serves as a consultant for Kite Pharma.
- Rakesh Awasthi, PhD – employee and stockholder at Novartis Pharmaceuticals.
- Dylan Bechtle, JD, MS – employee and stockholder at Johnson & Johnson.
- Mariette Boerstoel Streefland, MD, MBA – employee and stockholder at Bristol Myers Squibb.
- Wendy Corbett, PhD, MBA – employee and stockholder at Bristol Myers Squibb.
- Benjamin Dewees – formerly employed by Kyverna Therapeutics during the development of this paper; current employee and stockholder at Artiva Biotherapeutics.
- George Eastwood – employee of the Emily Whitehead Foundation, which has received event sponsorship from Novartis Pharmaceuticals Corporation.
- Julie Jadlowsky, PhD – serves as a consultant for BlueWhale Bio and is listed as an inventor on patents related to CAR T-cell therapies.
- Wendy Langeberg, PhD – employee at A2 Biotherapeutics, Inc.

- Erin Lee, RN, MSN – employee and stockholder at Johnson & Johnson.
- Lisa Joy Martin, PhD – employee and stockholder at Kite Pharma (a Gilead company).
- Amy Marshall, MPH – has served as a consultant for BlueWhale Bio.
- Gwen Nichols, MD – no competing interests to declare.
- Jamie Shapiro, PharmD – employee of Novartis Pharmaceuticals Corporation.
- Lana Shiu, MD – employee and stockholder at Kite Pharma (a Gilead company).
- Mark Stewart, PhD – no competing interests to declare.
- Nicholas Tschernia, MD – no competing interests to declare.
- Jennifer Willert, MD – employee of Novartis Pharmaceuticals Corporation.
- Hairong Xu, MD, PhD – employee and stockholder at Kite Pharma (a Gilead company).
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