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Multi-Stakeholder Qualitative Interviews to Inform Measurement of Patient Reported Outcomes After CAR-T

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Abstract

Toxicities after chimeric antigen receptor T cell (CAR-T) therapy are well known, yet the patient experience during and after CAR-T therapy has not been well described outside of the trial setting. We explored the patient experience after CAR-T therapy to inform the patient-reported outcomes (PRO) measurement approach for the Center for International Blood and Marrow Transplant Research (CIBMTR). We recruited (1) adult patients diagnosed with a hematologic malignancy 14 days to 6 months after receiving a commercial CAR T cell product who had agreed to be contacted by the CIBMTR, (2) caregivers of those patients, and (3) clinical experts in CAR-T therapy. Telephone interviews were conducted following a semistructured guide that included open-ended questions about symptoms and functioning. We conducted a systematic content analysis of each transcript using prespecified codes representing common domains of health, as well as open coding for emergent themes. Forty patients at 29 centers, 15 of their caregivers, and 15 experts from 9 centers participated, representing diversity with respect to age, sex, race/ethnicity, and years in practice (experts). Patients, caregivers, and experts shared largely consistent impressions of the patient experience after CAR-T therapy. Commonly described themes included anxiety, cognitive dysfunction, depression, fatigue, pain, impaired physical function, gastrointestinal symptoms, sexual dysfunction, sleep difficulties, need for support, financial impact, hospitalization, communication with healthcare providers, and the COVID-19 pandemic. Limitations in patients' ability to participate in social roles and activities was the most prevalent theme, found in nearly all interviews. In the setting of CAR-T therapy, a multidimensional approach to PRO measurement is needed that includes physical, mental, and social health, as well as the financial impact of this novel treatment. High-quality existing PRO tools are available to measure these concepts. Results will inform the CIBMTR measurement of

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SUPPLEMENTARY MATERIALS

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PROs after CAR-T therapy and may be applicable to other CAR-T studies that aim to represent patient experiences.

Keywords

Chimeric antigen receptor T cell therapy; Qualitative; Patient experience; Patient-reported outcomes

INTRODUCTION

Patient-reported outcomes (PROs)—patients' reporting of their own symptoms and functioning without interpretation by anyone else [1]—is an important component of evaluating new therapies and optimizing patient care. In the setting of hematopoietic cell transplantation (HCT), a treatment option for cancers and other diseases, PRO measures have gained acceptance [2,3] as outcomes that complement traditional survival endpoints. The Center for International Blood and Marrow Transplant Research (CIBMTR) maintains a clinical outcome registry including longitudinal follow-up for more than 575,000 transplantation and cellular therapy recipients [4]. The CIBMTR developed an infrastructure for the routine collection of PRO measures and solicited multidisciplinary expert input to inform a measurement strategy, which includes collection of a core set of domains and time points suitable for longitudinal measurement before and after transplantation [5].

Numerous PRO measures are available, and although different measures may be appropriate for different contexts, the proliferation of measures makes comparisons across studies and populations difficult. The Patient-Reported Outcomes Measurement Information System (PROMIS) is the NIH's initiative to standardize measurement of common PROs in clinical research across chronic conditions [6], including oncology [6,7]. PROMIS offers a publicly available, flexible set of tools that use advances in qualitative [8], cognitive [9], and psychometric [10] research methodologies. A critical advantage of PROMIS is the ability to deliver measures using computerized adaptive testing (CAT) [11], where the questions a person answers are tailored individually based on previous responses, to reduce the response burden. In a context of long-term follow-up, where symptoms and functioning are expected to vary widely both over time and across individuals, CAT may better represent the full range of symptomatology and functioning (eg, reduced floor and ceiling effects) while not over-burdening patients with multiple long measures.

The CIBMTR is using PROMIS measures in the transplantation setting [12]; however, foundational methodological work has not been conducted in the context of newer cellular immunotherapies, such as chimeric antigen receptor T cell (CAR-T) therapy. In CAR-T therapy, a patient's T cells are genetically engineered in vitro to be directed against cancer cells [13]. Although promising results have been noted in patients with hematologic malignancies [14-16], these therapies are associated with specific toxicities that may affect quality of life. A recent review of PRO measures in studies of patients receiving CAR-T therapy found that CAR-T clinical trials have used a variety of PRO measures, including the EORTC QLQ-C30, the FACT-Lym, the PRO-CTCAE, and PROMIS [17]. The review authors made recommendations for PRO measurements in future studies,

including that PROMIS measures be considered for physical functioning and disease symptoms complemented by items from the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) for measurements of symptomatic adverse events during the acute phase of treatment. Importantly, the review advocated for qualitative studies to include patients' input on measured domains and instruments [17]. Qualitative studies also can provide evidence of a measure's content validity, including its relevance, comprehensiveness, and comprehensibility [18].

The objective of the present study was to use qualitative methods to directly involve stakeholders in determining a PRO measurement plan for the CIBMTR and to evaluate the relevance and comprehensiveness of PROMIS domains previously selected for the transplantation setting in the new context of CAR-T therapy.

METHODS

This was a nonrandomized prospective cross-sectional qualitative interview study with 3 groups of stakeholders: patients, caregivers of patients, and CAR-T experts. Eligible patients were English-speaking adults age ≥18 years diagnosed with a hematologic malignancy who had received a commercial CAR-T product and were between 14 days and 6 months post-therapy. Patients who met these eligibility criteria and had consented to be contacted by the CIBMTR were sent an informational letter via email describing the study and inviting them to participate. Interested caregivers referred by their patients were approached by phone and/or email for participation. Eligible patients and caregivers who agreed to participate provided verbal consent.

CAR-T experts were defined as clinicians or researchers who had at least 2 years of experience treating or managing recipients of CAR-T therapy. These included physicians (some of whom were also trialists/clinical researchers), advanced practice providers, and registered nurses. Experts were identified in 2 ways; one half were identified by the research team through snowball sampling and the other half were identified via a systematic literature search for first or senior authors of manuscripts relating to CAR-T therapy published in leading journals between 2019 and 2021: *Journal of Clinical Oncology, New England Journal of Medicine, Blood, Leukemia*, and *Blood Advances*. Experts were recruited by email and screened for eligibility using a brief demographic questionnaire. An informational consent letter was emailed to participating experts.

Within each stakeholder group, we aimed for a diverse sample of participants with regard to age, sex, and race/ethnicity. For experts, we also aimed for diversity in terms of the role of provider (MD vs advanced practice provider) and years in practice. For patients, we also aimed for diversity with regard to infusion type, setting (inpatient and/or outpatient), and time since CAR-T therapy.

Data Collection

A trained interviewer conducted qualitative interviews by Zoom audio or phone following a semistructured guide aligned with standards for content validity as outlined by PROMIS, COnsensus-based Standards for the selection of health Measurement Instruments

(COSMIN), and ISPOR [8,19,20]. The guide included open-ended questions for concept elicitation and questions about the impact of CAR-T therapy on daily life (Table 1). For caregiver interviews, questions referenced the patient's experience from the caregiver's perspective. Expert interviews covered similar topics, with questions about patients in the aggregate. Stakeholders were interviewed once; no PRO assessments were administered. Interviews were audio recorded and transcribed. Compensation of up to $75 was offered to patients, caregivers, and experts for their time.

Statistical Methods

We conducted a systematic content analysis of each transcript using a combination of prespecified codes and open coding [21]. Prespecified codes included domains of life expected to be affected by CAR-T therapy and represented by PROMIS item banks [6] and the COST-FACIT measure [22]. Open coding included a catalog of any additional symptoms or experiences not reflected in the prespecified domains. We used published PROMIS domain definitions where applicable with some modifications, as noted in Table 2. For financial impact, we built on the domain definition of the COST-FACIT [22], a PRO measure that assesses self-reported financial distress experienced by cancer patients to screen for financial toxicity, including out-of-pocket costs and loss of income or economic changes caused by treatments and disease. For our coding purposes, we included all mentions of costs and finances, not just financial toxicity.

We coded patient interviews with regard to whether the experience happened in the previous week in order to examine experiences of symptoms at different time points after CAR-T therapy. Four members of our team, representing both clinical and methodological expertise, read 2 transcripts and discussed a high-level summary of themes to develop a preliminary codebook. To facilitate team-based coding, our code-book included a code name, a definition, inclusion and exclusion criteria to help distinguish codes from one another, and examples [23]. In general, we coded the presence of symptoms, such that if a patient said they felt depressed, this was included under the code of depression, but if a participant mentioned that they did not feel depressed, this was not coded under depression. The exception to this was the code for financial impact, which we used to categorize comments related to costs and insurance, regardless of whether or not the participant described it as a negative impact. We independently double-coded 10% of transcripts, meeting regularly as a team to identify coding discrepancies and adjust the preliminary code-book as needed to create a final codebook. Meaningful changes were related to new codes that were added. Three team members coded all transcripts using the final codebook. Transcripts were managed using NVivo (release 1.5) qualitative analysis software. Herein we describe the themes represented in the interviews along with the similarities and differences within and across stakeholder groups based on prevalence of codes by role, and for patients we also report prevalence of codes by duration of time since CAR-T treatment. This study was approved by the National Marrow Donor Program/Be The Match Institutional Review Board.

RESULTS

Recruitment occurred between April 1, 2021, and December 15, 2021. Participants included 40 patients at 29 centers who received a commercial CAR-T product for a hematologic malignancy during 2020 or 2021, 15 caregivers, and 15 experts from 9 centers. Participants were diverse with respect to sex, age, race/ethnicity, caregiver relationship to patient, and expert role and years in practice (Table 3). Patients described a wide range of experiences after CAR-T therapy, ranging from very difficult experiences with many side effects to very few side effects. Patients, caregivers, and experts shared consistent impressions of the patient experience after CAR-T therapy, as evidenced by the codes generally being used consistently across roles (Table 2). Other than the codes that were unique to either caregivers (caregiver perspective) or experts (PRO measures and treatment procedures), there were no codes that were used exclusively by a particular role. Representative quotations for each code by role are available in the Supplementary Data.

Mental Health

Mental/cognitive health was an important theme. Cognitive problems, particularly forgetfulness, were common overall although varying somewhat by role, with all experts (100%) referencing cognitive function and somewhat fewer patients (60%) and caregivers (47%) mentioning it. Cognitive function was mentioned as a recent issue (ie, experienced within the last 7 days) for some patients at 2 to 4 months post-CAR-T therapy and 4 to 6 months post-CAR-T therapy, but not by any patients at 14 days to 2 months post-CAR-T therapy. Depression was mentioned in approximately 40% of interviews. One caregiver described their spouse’s mental health experience with cognitive dysfunction and depression, “He kind of didn’t have any interest in interacting with anyone else. I think that he kind of got into a…I guess, depression. He was frustrated with himself all the time because he couldn’t remember anything." Depression was mentioned as a recent issue by patients at all time points since CAR-T therapy. Anxiety was common, mentioned by a total of 17 patients (~40%), but only 3 patients mentioned it as a recent issue, all of whom were at 2 to 4 months post-CAR-T therapy and had upcoming positron emission tomography scans. One of these 3 patients also described anxiety specifically related to financial stress from being unable to work and disability compensation providing only approximately $100 per month. Psychosocial illness or treatment impact was one of the most frequently mentioned concepts, coded in >75% of interviews, with people describing how the experience changed them; for example, “it affected me for the better, I think, because it opened my eyes to see not everything is rainbows and roses.”

Physical Health

Within the theme of physical health, the most commonly coded topic across all stakeholders was fatigue, with almost three-quarters of experts and caregivers mentioning it, as well as 60% of patients. Most commonly noted by patients were physical limitations and pain, although the experience of pain seemed related to past damage from the underlying disease (eg, bone pain). Fatigue, physical limitations, and pain were all mentioned as recent issues by patients at all time points post-CAR-T therapy. More than one-half of participants mentioned gastrointestinal (GI) symptoms, in particular lack of appetite. GI symptoms were

mentioned as a recent issue for some patients at 2 to 4 months post-CAR-T and 4 to 6 months post-CAR-T but not by any patients at 14 days to 2 months post-CAR-T. Difficulty sleeping (often because of pain), as well as sleeping more than usual and needing to nap, were mentioned by nearly all caregivers but by fewer patients and experts. Sexual function and fertility were mentioned in the fewest interviews (<10%).

Social Health

Almost all participants acknowledged impacts to social roles and activities as a result of receiving CAR-T therapy; for example, the patient who explained that needing to nap means "I have to take extra breaks. And it's impacted the level of work that I'm able to accomplish. So I'm not able to get to as many clients throughout the day as I did pre-CAR-T." Impacts on social roles were mentioned as a recent issue for patients at 2 to 4 months post-CAR-T but not at 14 days to 2 months or 4 to 6 months post CAR-T.

Similarly, the overwhelming majority of patients, caregivers, and experts acknowledged social support was impacted by CAR-T therapy. One patient explained "I think in some cases, the relationships are better. They've stepped up to help take care of me and be there for me on days when I'm sad." According to one expert, "most of our patients have really good support groups. They understand support systems. They understand that they need a constant companion directly after CAR-T therapy. And for most patients, they have that. And I think the families are very supportive." Although impacts were mostly expressed as positive, participants also referenced the patient's inability to physically connect with family and friends owing to the Coronavirus disease 2019 (COVID-19) pandemic and the lower immunity of the patient. One patient mentioned that "I talk and I communicate by Zoom, and by phone, and Whatsapp videos. So it's another kind of communication. Of course, it's not a hug that I can give to my friends but at least we are communicating. But I can deal with it because we have other means of communication." Some caregivers mentioned that it was stressful caring for the patients especially during the pandemic, with one caregiver explaining "…especially during COVID when you don't have any help, and I can't bring people into the house, when family can't visit to take the load off of you. It's all-encompassing." Social support was mentioned as a recent experience by patients at all time points post-CAR-T therapy.

Financial Impact

The financial impact of CAR-T therapy was noted by >80% of participants overall, although not as a recent issue except by 1 patient at 2 to 4 months post-CAR-T therapy. Participants described concerns about out-of-pocket costs and loss of income or economic changes caused by treatments and disease. One patient explained, "you need to have somewhere to stay. I had to continue to pay for car insurance, pay for my vehicle, pay for activities that my child has. So, it was very difficult."

Other

Under Emergent Symptoms, we coded any symptoms or experiences that participants mentioned that were not represented by the already-defined symptom/function codes. Fever

was mentioned the most frequently, followed by dizziness and/or hypotension and balance issues. Multiple patients experienced hair loss that came as a surprise.

Open-coding resulted in 3 codes regarding experiences of CAR-T therapy. Communication with the care team was coded in all patient interviews (100%) and the majority of caregiver interviews (80%) but in only 1 expert interview (7%). Patients described predominantly positive communication with providers, referencing the help communicating with their care team provided. Some patients described problems communicating with care team members, including difficulty knowing how to approach a topic. Hospitalization was coded in 56% of all interviews, with 80% of patients acknowledging hospital and/or intensive care unit stays. Because of the timing of these interviews, COVID-19 and the pandemic were frequently mentioned.

We used a caregiver perspective code to note the unique perspectives of caregivers. Multiple caregivers mentioned feeling unprepared by their care team for the difficulty taking care of the patient. We also applied the caregiver perspective code to comments from caregivers that highlighted issues they noticed that the patients did not. For example, one caregiver noted a change in the patient's personality, "I don't know if he realizes his patience has been shorter."

Two codes were unique to experts: use of PRO measures in practice or research and CAR-T treatment procedures. First, we asked providers about whether they used PRO measures in practice and/or research. Most did not have PRO measures available to guide clinical care, though 1 physician expert reported institution-wide PROs used for clinical care (using the PRO CTCAE) and remarked on its usefulness, "it also helps to guide the conversation for them, because sometimes I'm like, 'Oh, how are you doing?' And the patient is like, 'I'm fine.' And they don't bring up anything. [laughter] And then I'm like, 'Well, on the form that you filled out, you mentioned that you have decreased appetite or trouble drinking fluids. Can you tell me about that?' So it has clinical impact." A nurse practitioner expert mentioned wishing they had information about patients' social determinants of health: "a resource question would be helpful to ask, such as resources for food, transportation, and housing."

We asked experts about CAR-T therapy procedures regarding inpatient/outpatient treatment options. Most experts mentioned having both options at their centers with treatment being dependent on the regimen the patient received. Experts acknowledged that current treatment procedures have a significant impact on patients' social and financial health. For most centers, inpatient treatment procedures require patients to stay in the hospital for 7 to 14 days after CAR-T therapy. One expert mentioned that "we ask patients to stay within an hour of our treatment center, as do just about all places—within 1 to 2 hours. Patients who come from far away have to pick up and move to be close by, at least for 4 to 6 weeks."

Measurement Gaps

In general, the existing CIBMTR PRO measurement system is well-poised to capture the symptoms and functioning of patients after CAR-T therapy, with a measurement approach that includes anxiety, cognitive function, depression, fatigue, pain, physical function, sexual

function, sleep, social roles and activities, emotional support, and financial impact (Table 2). There are additional concepts identified by these interviews that could be measured using either existing PROMIS banks (eg, GI symptoms) and/or with PRO-CTCAE items (eg, dry mouth, rash). A small number of symptoms were mentioned that could not be measured with either PROMIS or PRO-CTCAE (eg, sensitivity to sound).

DISCUSSION

In this large qualitative interview study with patients, their caregivers, and CAR-T experts, we explored the patient experience after CAR-T therapy. Patients described the effects of CAR-T therapy on their physical, mental, and social health; the financial impact; and communication with healthcare providers. Caregivers and experts also described the effects of CAR-T therapy on patients, providing similar accounts as those of the patients.

The physical, mental, and social health of patients in our study were impacted after CAR-T therapy, with patients experiencing pain, fatigue, GI symptoms, physical limitations, and difficulties with cognitive, emotional, and social functioning. Our findings are similar to those of Cheng et al. [24], who conducted a focus group with 18 adult patients who were further from their CAR-T therapy (6 months to 2.5 years) than our patients (2 weeks to 6 months) but nevertheless described impairments in social, emotional, and physical functioning following CAR-T therapy, with participation in social roles and activities the concept most frequently mentioned in both samples [24]. A qualitative interview study of 10 patients and 4 caregivers identified 3 themes associated with the CAR-T therapy experience: (1) communication with healthcare professionals, (2) social isolation, and (3) wide variation in treatment toxicities, with common side effects including fever, fatigue, reduced appetite, and memory/cognition problems [25], each of which was a key theme in our study as well.

Because the CIBMTR intends to measure PROs longitudinally before and after CAR-T therapy, we intentionally explored the patient experience at varying time points from when patients received their CAR-T infusion. Our findings echo those of Whisenant et al. [26], who found that recipients of CAR-T therapy experienced numerous physical and emotional symptoms as well as interference with social activities and relationships, but that these experiences varied depending on time since CAR-T therapy. Fatigue, pain, depression, and physical limitations were consistently affected in the months following CAR-T, whereas GI symptoms, anxiety, cognitive function, and social roles were more often reported by patients further out from treatment (2 to 6 months).

Patients in our study who were 14 days to 2 months from CAR-T therapy did not report any recent cognitive function or GI side effects. Previous studies have shown that cognitive function and GI side effects typically begin within the first week after receipt of CAR-T therapy, with most patients recovering by 1 month post-therapy [27-30]. Because patients in this study were invited to participate via email, one possible explanation for the lack of GI and cognitive function side effects in the group who was less than 2 months post-CAR-T is that patients who had more serious side effects were more unwell and thus less likely to respond to our outreach attempts.

Our study also included caregiver and expert perspectives and found them to be similar to patients' accounts of their experience. Expert perspectives were important for ensuring that the planned CIBMTR measurement approach meets the needs of the research community.

As hypothesized, the majority of the symptoms and functioning described by patients, caregivers, and experts are measurable by the PROMIS measurement system selected by the CIBMTR and already included in its PRO infrastructure. These results provide evidence of the content validity of the CIBMTR's measurement approach in the context of CAR-T therapy. We identified few gaps in CIBMTR's PRO measurement plan. Additional concepts that were mentioned by multiple participants that the CIBMTR will consider adding to its PRO battery for CAR-T recipients are headache, dizziness, neuropathy, diarrhea, and nausea/lack of appetite. All of these could be measured with PROMIS or the PRO-CTCAE. Although some have recommended that PRO measures be administered before lymphodepletion, at least weekly after CAR-T therapy, monthly until 1 year, and yearly thereafter [17]; this frequency of data collection is not currently feasible for the large-scale data collection effort at the CIBMTR. The time points for PRO measurement for HCT recipients are pretransplantation and 100 days, 180 days, and yearly thereafter post-transplantation, coinciding with the time points at which clinical data are collected. The CIBMTR added an additional earlier time point for CAR-T recipients at 1 month, as initial recovery is quicker after CAR-T therapy than after transplantation. Future adjustments to customize the content included at each time point will be considered as PRO data are collected and analyzed.

This study has some limitations. Our sample included patients who agreed to be contacted by the CIBMTR and were comfortable speaking English, and thus it is not generalizable to all patients who receive CAR-T therapy. We aimed to enroll a diverse sample of patients and caregivers to represent the population of CAR-T recipients as much as possible, although it was more difficult to recruit patients who had received treatment more recently (2 weeks to 2 months post-therapy) because fewer of these patients responded to our outreach attempts. Some of the physical and emotional symptoms reported by patients in our sample might have been experienced before CAR-T therapy, because of the patient's underlying disease or previous treatments. We asked questions about symptoms experienced after CAR-T therapy, but we purposefully did not ask patients to attribute their symptoms to CAR-T therapy, their underlying disease, or anything else, while recognizing that it may be difficult for them to do so.

The patient experience after CAR-T therapy is widely variable but marked by difficulties with mental and cognitive health, social health, and financial concerns. Physical symptoms are also an issue for many patients. Existing patient-reported measurement systems, PROMIS in particular, are appropriate for capturing the predominant symptom and function domains impacted by CAR-T therapy. These results will inform the CIBMTR strategy for PRO measurement and are applicable to other CAR-T studies that aim to represent patient experiences using PRO tools. Furthermore, they may help guide consistency in the field regarding PRO assessment in the setting of CAR-T therapy.

Data use statement:

The CIBMTR supports accessibility of research in accordance with the National Institutes of Health's Data Sharing Policy and the National Cancer Institute's Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases deidentified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for Industry: Patient-reported outcome measures: use in medical product development to support labeling claims. Published online 2009. Available at: https://www.fda.gov/media/77832/download. Accessed July 13, 2022.
2. Shaw BE. Graft-versus-host disease clinical trials: is it time for patients centered outcomes to be the primary objective? Curr Hematol Malig Rep. 2019;14:22–30. [PubMed: 30637541]
3. Shaw BE, D'Souza A, Lee SJ. Importance of assessing patient-reported outcomes with salvage autologous transplantation in relapsed multiple myeloma. J Clin Oncol. 2019;37:1598–1600. [PubMed: 31084545]
4. Jensen RE, Snyder CF, Abernethy AP, et al. Review of electronic patient-reported outcomes systems used in cancer clinical care. J Oncol Pract. 2014;10:e215–e222. [PubMed: 24301843]
5. Cusatis R, Flynn KE, Vasu S, et al. Adding centralized electronic patient-reported outcome data collection to an established international clinical outcomes registry. Transplant Cell Ther. 2022;28:112.e1–112.e9.
6. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010;63:1179–1194. [PubMed: 20685078]
7. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol. 2007;25:5106–5112. [PubMed: 17991929]
8. DeWalt DA, Rothrock N, Yount S, Stone AA. Evaluation of item candidates: the PROMIS qualitative item review. Med Care. 2007;45(5 suppl):S12–S21. [PubMed: 17443114]

9. Irwin DE, Varni JW, Yeatts K, DeWalt DA. Cognitive interviewing methodology in the development of a pediatric item bank: a patient reported outcomes measurement information system (PROMIS) study. Health Qual Life Outcomes. 2009;7:3. 10.1186/1477-7525-7-3. [PubMed: 19166601]
10. Reeve BB, Hays RD, Bjorner JB, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care. 2007;45(5 suppl 1):S22–S31. [PubMed: 17443115]
11. Cella D, Gershon R, Lai JS, Choi S. The future of outcomes measurement: item banking, tailored short-forms, and computerized adaptive assessment. Qual Life Res. 2007;16(suppl 1):133–141. [PubMed: 17401637]
12. Shaw BE, Lee SJ, Horowitz MM, Wood WA, Rizzo JD, Flynn KE. Can we agree on patient-reported outcome measures for assessing hematopoietic cell transplantation patients? A study from the CIBMTR and BMT CTN. Bone Marrow Transplant. 2016;51:1173–1179. [PubMed: 27159181]
13. American Cancer Society. CAR T-cell therapy and its side effects. Available at: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html. Accessed July 14, 2022.
14. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378:439–448. [PubMed: 29385370]
15. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45–56. [PubMed: 30501490]
16. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531–2544. [PubMed: 29226797]
17. Chakraborty R, Sidana S, Shah GL, Scordo M, Hamilton BK, Majhail NS. Patient-reported outcomes with chimeric antigen receptor-T cell therapy: challenges and opportunities. Biol Blood Marrow Transplant. 2019;25: e155–e162. [PubMed: 30500439]
18. Prinsen CAC, Mokkink LB, Bouter LM, et al. COSMIN guideline for systematic reviews of patient-reported outcome measures. Qual Life Res. 2018;27:1147–1157. [PubMed: 29435801]
19. Terwee CB, Prinsen CAC, Chiarotto A, et al. COSMIN methodology for evaluating the content validity of patient-reported outcome measures: a Delphi study. Qual Life Res. 2018;27:1159–1170. [PubMed: 29550964]
20. Rothman M, Burke L, Erickson P, Leidy NK, Patrick DL, Petrie CD. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO task force report. Value Health. 2009;12:1075–1083. [PubMed: 19804437]
21. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005;15:1277–1288. [PubMed: 16204405]
22. de Souza JA, Yap BJ, Wroblewski K, et al. Measuring financial toxicity as a clinically relevant patient-reported outcome: the validation of the COmprehensive Score for financial Toxicity (COST). Cancer. 2017;123:476–484. [PubMed: 27716900]
23. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook development for team-based qualitative analysis. CAM Journal. 1998;10:31–36.
24. Cheng R, Scippa K, Locke FL, Snider JT, Jim H. Patient perspectives on health-related quality of life in diffuse large B-cell lymphoma treated with CAR T-cell therapy: a qualitative study. Oncol Ther. 2022;10:123–141. [PubMed: 34778941]
25. Stenson CL, Vidrine J, Dewhurst F, Osborne W, Menne T, Stocker R. A qualitative service evaluation of patient and caregiver experiences of CAR-T therapy: recommendations for service development and implications for palliative care teams. Palliat Med. 2023;37:215–220. [PubMed: 36428287]
26. Whisenant MS, Srour SA, Williams LA, et al. The unique symptom burden of patients receiving CAR T-cell therapy. Semin Oncol Nurs. 2021;37:151216. [PubMed: 34629213]
27. Zahid A, Siegler EL, Kenderian SS. CART cell toxicities: new insight into mechanisms and management. Clin Hematol Int. 2020;2:149–155. [PubMed: 33409484]
28. Penack O, Koenecke C. Complications after CD19+ CAR T-cell therapy. Cancers (Basel). 2020;12:3445. [PubMed: 33228221]

29. Gust J, Taraseviciute A, Turtle CJ. Neurotoxicity associated with CD19-targeted CAR-T cell therapies. CNS Drugs. 2018;32:1091–1101. [PubMed: 30387077]

30. Abu-Sbeih H, Tang T, Ali FS, et al. Gastrointestinal adverse events observed after chimeric antigen receptor T-cell therapy. Am J Clin Oncol. 2019;42:789–796. [PubMed: 31478934]

Table 1

Summary of Interview Content with Example Questions

Category	Example Clinician/Expert Questions	Example Patient Questions
Elicitation of current symptoms, any side effects, and general impact	• What are the most common symptoms or side effects that your patients have experienced after CAR-T therapy? • What are the serious side effects that your patients have experienced? • What do you think are the symptoms that are most important/significant to patients?	• How have you felt physically over the past 7 days? • How have your thinking and emotions been in the past 7 days? • Have you had any side effects from the CAR-T therapy? • How did receiving CAR-T therapy affect your life?
Impact of physical, emotional, and cognitive symptoms	Tell me a little more about the symptoms that patients have: • Physical • Emotional • Cognitive	• You mentioned [physical, emotional, cognitive concept]: • How does [concept] affect your daily life? • Have you ever talked to your doctor or someone else on your health care team about [concept]? • How has [concept] changed since you received the CAR-T infusion?
Social impact	How does receiving CAR-T therapy impact patients' • Relationships with family and friends? • Ability to participate in social activities?	• What about your relationships with your family and friends or your ability to go to work or school or do other things that you would like to do. How have these things been affected? • How does [concept] affect your daily life? • Have you ever talked to your doctor or someone else on your health care team about [concept]? • How has [concept] changed since receiving CAR-T infusion?
Financial Impact	• How does receiving CAR-T therapy impact patients financially?	Let's talk about the financial impact of CAR-T therapy. • Can you tell me what that has been like for you? • Are there other costs apart from the treatment cost that you have to deal with? • Have you had to make changes in your life because of costs?

Table 2

Prevalence of Codes During Interviews, Overall and by Participant Role and Patient Time Point

Theme or Code	Description of Code	Total Number of Interviews Containing Code (N = 70)	Role, n			Experienced in the Past 7 days, n			CIBMTR ePRO
			Experts (N = 15)	Caregivers (N = 15)	Patients (N = 40)	14 d to 2 mo Post-CAR-T (N = 10)	2-4 mo Post-CAR-T (N = 15)	4-6 mo Post-CAR-T (N = 15)	
Mental Health									
Anxiety	PROMIS Anxiety assesses self-reported fear, hyperarousal, and somatic symptoms that reflect autonomic arousal and experience of threat.	37	11	9	17	0	3	0	Y
Cognitive function	PROMIS cognitive function assesses self-reported mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions.	46	15	7	24	0	4	1	Y
Depression	PROMIS Depression assesses self-reported negative mood, self-criticism, interpersonal alienation, and decreased positive affect and engagement.	27	6	5	16	1	2	1	Y
Psychosocial illness or treatment impact	PROMIS Psychosocial Illness impact accesses direct negative and positive psychosocial effects of cancer, distinct from general emotional distress. We also included psychosocial impacts of cancer treatments.	55	11	9	35	1	0	0	N
Physical Health									
Fatigue	PROMIS Fatigue ranges from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to execute daily activities and function normally.	46	11	11	24	2	2	5	Y
Gastrointestinal symptoms	PROMIS Gastrointestinal (GI) symptoms include gastroesophageal reflux, disrupted swallowing, diarrhea, bowel incontinence/soilage, lack of appetite/nausea and vomiting, constipation, belly pain, and gas/bloat/flatulence.	38	8	10	20	0	1	3	N
Pain	PROMIS Pain Interference assesses self-reported consequences of pain on daily life.	28	4	5	19	1	3	3	Y
Physical function	PROMIS Physical Function assesses self-reported capability of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands.	42	5	7	30	2	3	3	Y
Sexual function, menopause, and fertility	PROMIS Sexual Function assesses self-reported interest, function, and satisfaction with sexual activity. We also included reproductive issues/fertility and menopause.	5	1	1	3	0	0	1	Y

Theme or Code	Description of Code	Total Number of Interviews Containing Code (N = 70)	Role, n			Experienced in the Past 7 days, n			CIBMTR ePRO
			Experts (N = 15)	Caregivers (N = 15)	Patients (N = 40)	14 d to 2 mo Post-CAR-T (N = 10)	2-4 mo Post-CAR-T (N = 15)	4-6 mo Post-CAR-T (N = 15)	
Sleep disturbance and sleep-related impairment	PROMIS Sleep Disturbance assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. Sleep-related impairment assesses perceptions of alertness, sleepiness, and tiredness during usual waking hours.	23	2	8	13	0	1	1	Y
Social Health									
Social roles and activities	PROMIS Ability to Participate in Social Roles and Activities assesses the perceived ability to perform one's usual social roles and activities, including work.	69	15	15	39	0	4	0	Y
Social support	PROMIS social health domains cover companionship, emotional support, informational support, and instrumental support.	65	13	13	39	1	1	2	Y
Financial impact	The COST-FACIT measure assesses self-reported financial distress experienced by cancer patients to screen for financial toxicity, including out-of-pocket costs and loss of income or economic changes caused by treatments and disease. We included all mentions of costs and finances, not just financial toxicity.	57	14	12	31	0	1	0	Y
Other									
Emergent symptoms	We used this code to catalog symptoms or experiences not covered by already defined symptom/function codes: fever, dizziness/hypotension/balance, hallucinations, neuropathy, headache, dyspnea, fast heart rate, cough, weight loss, dry throat, dry skin, flaking skin, sensitive skin, scalp itching, scalp pain, rash, fever blisters/cold sores, bad taste or lack of taste, joint swelling, mouth sores, mouth infection, urinary tract infection, cellulitis, sleep talking, hot feet, hot flashes, eye floaters/flashes, seizure, tinnitus, sensitivity to sound, hair loss, negative emotions (frustration, anger, feeling overwhelmed, impatience, and paranoia).	62	15	12	35	1	5	4	N
Communication with healthcare providers	Encompasses conversations with providers, lack of conversations with providers, and patient expectations about communication.	53	1	12	40	0	0	0	N
Hospital/ICU admission	Hospitalization (planned or unplanned) and ICU admissions	39	3	4	32	0	0	0	N
COVID-19	Any reference to COVID-19 or the pandemic, including anxiety due to COVID-19	49	7	12	30	0	0	0	N
Caregiver perspective	Unique caregiver perspective on patient's symptoms	8	N/A	6	2	N/A	N/A	N/A	N
PRO measure	Use of PRO measures in clinical practice and research	15	15	N/A	N/A	N/A	N/A	N/A	N

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Theme or Code	Description of Code	Total Number of Interviews Containing Code (N = 70)	Role, n			Experienced in the Past 7 days, n			CIBMTR ePRO
			Experts (N = 15)	Caregivers (N = 15)	Patients (N = 40)	14 d to 2 mo Post-CAR-T (N = 10)	2-4 mo Post-CAR-T (N = 15)	4-6 mo Post-CAR-T (N = 15)	
Treatment procedures	Institutional procedures for CAR-T therapy and its impact, which includes not driving for 60 days, 90-day PET scan, 28 days hospitalization, etc.	12	12	N/A	N/A	N/A	N/A	N/A	N

N/A indicates that a particular code was not relevant for that role; ICU, intensive care unit; PET, position emission tomography.

Table 3

Characteristics of Participants (N = 70)

Characteristics	Expert(N = 15), n (%)	Caregiver (N = 15), n (%)	Patient(N = 40), n (%)
Sex			
Male	6 (40)	4 (27)	23 (58)
Female	9 (60)	11 (73)	17 (42)
Age			
18-25 yr	11 (73)	0 (0)	4 (10)
26-64 yr	1 (7)	12 (80)	23 (58)
>65 yr	3 (20)	3 (20)	13 (32)
Race			
White	11 (73)	14 (93)	27 (67.5)
Black or African American	1 (7)	1 (7)	4 (10)
Asian	3 (20)	0 (0)	5 (12.5)
American Indian or Alaska Native	0 (0)	0 (0)	2 (5)
More than 1 race	0 (0)	0 (0)	1 (2.5)
Other	0 (0)	0 (0)	1 (2.5)
Ethnicity			
Hispanic or Latino	0 (0)	3 (20)	7 (18)
Not Hispanic or Latino	15 (100	12 (80)	33 (82)
Infusion setting type			
Inpatient	N/A	N/A	35 (87)
Outpatient	N/A	N/A	5 (13)
Relationship to patient			
Spouse	N/A	9 (60)	N/A
Non-spouse	N/A	6 (40)	N/A
Role*			
Physician/transplantation oncologist	9 (60)	N/A	N/A
Advanced practice provider	3 (20)	N/A	N/A

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Characteristics	Expert(N = 15), n (%)	Caregiver (N = 15), n (%)	Patient(N = 40), n (%)
Registered nurse	3 (20)	N/A	N/A
Trialist/clinical researcher	6 (40)	N/A	N/A
Years in practice			
2-10 yr	7 (47)	N/A	N/A
10+ yr	8 (53)	N/A	N/A

*Numbers do not add to 100%; the 6 trialist/clinical researcher participants were also MDs.N/A indicates not applicable.