Chimeric Antigen Receptor (CAR) T-Cell Therapy and Patient Reported Outcomes (PROs)

Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

August 22, 2018

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Meeting Purpose

Obtain MEDCAC recommendations regarding

- **how existing PRO assessment tools should be incorporated into future clinical studies, including future clinical studies on CAR T-cell therapy; and**

- **clinical study design characteristics, study duration, and suitable study controls.**

Voting Question #1

- *How confident are you that each of the following PRO assessments are valid and generalizable to the Medicare population:
  a. Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE);
  b. MD Anderson Symptom Inventory (MDASI);
  c. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30);
  d. University of Washington Quality of life (UW-QOL);
  e. Patient-Reported Outcome Measurement Information System (PROMIS);
  f. Electronic Self-Report-Cancer (ESRA-C);
  g. Functional Living Index-Cancer (FLIC).

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Confidence — Intermediate — High Confidence

* CMS recognizes the importance of mortality as a meaningful primary health outcome of interest in research studies. We are seeking input on patient-reported outcomes to be considered.

PRO-CTCAE

- Developed in 2008 to supply meaningful data and improve understanding of symptomatic adverse events (AEs) from multiple disease states.
- Contains 78 symptomatic AEs from more than 800 terms.
- Electronic system of data collection for both clinical trial workflow and user-experience.
- **Validity:** demonstrated in large heterogeneous sample of patients undergoing cancer treatment (n=940), where most items exhibited significant ($p<.05$) effect size and test-retest reliability (Dueck et al., 2015).
- Each term contains 1-3 items to attribute frequency, severity, and interference with corresponding CTCAE symptom, with independent unique contribution from each attribute (Mitchell et al., 2012).

MDASI

- Developed in 2000 from established inventories for clinical and research use to assess cancer patients' symptom severity and interference with daily living.
- Contains 13 core symptom items and 6 interference items, with disease, site, and treatment specific modules available.
- Paper, electronic, and telephone based formats all shown to be equally effective for both clinical trial workflow and user-experience.
- **Validity:** symptom interference but not severity differed among patients receiving bone marrow transplant, chemotherapy, or no treatment (Cleeland et al., 2000) with strong internal consistency statistics.
- Core items tested in 100 multiple myeloma and Non-Hodgkin lymphoma patients scheduled for autologous stem cell transplantation also demonstrated strong internal reliability (Anderson et al., 2007).

EORTC-QLQ-C30

- Developed in 1991 as stand-alone multi-dimensional questionnaire covering issues important for all cancer patients.

- Contains 6 functional scales, 3 symptom scales, and 8 single item scales, with additional disease specific modules and computerized adaptive testing measures available.

- **Validity:** shown by reliable correlations among quality of life scales with clear discrimination among performance status and treatment toxicity. There were statistically significant changes in physical and role functioning and global quality of life (Aaronson et al., 1993).

- Use of EORTC measures facilitates and improves communication between patients and healthcare professionals (Kotronoulas et al., 2014).

UW-QOL

- Developed in 1993 as assessment of quality of life in head and neck cancer patients.

- Contains 12 domains reported using 2 subscales (physical and social-emotional function).

- **Validity (Quantitative):** evaluated as a constructive measure, containing items of desired content, and relates well to other tests of similar constructs for patients outcome following oral cancer surgery and in screening for multidisciplinary intervention of physical dysfunction (Rogers et al., 2008 and 2009).

- The UW-QOL is correlated with the emotional and aspects of physical functioning domains from EORTC-QLQ-C30, in 290 primary cancer patients. Mood and anxiety scores were associated with patient age ($p=0.005$, $p<0.001$, Rogers et al., 2002).

PROMIS

- Described in 2007 as using item response theory to present health measures in computer adaptive testing format from other established PRO assessments (DeWalt et al., 2007).

- Contains over 700 measures in 5 profile domains (physical function, fatigue, pain, mental & social health)

- Modular structure such that customization can be built at the measure level, as all measures in PROMIS profiles can be administered individually

- **Validity:** identified for all PROMIS domains evaluated across 6 clinical populations (CHF, COPD, RA, cancer, back pain, and major depression) for approximately 1,500 individuals (Cook et al., 2016).

- Emphasizes domain-specific over disease-specific measurement, and recognized function of PROMIS in real-world clinical settings (Cook et al., 2016).

ESRA-C

- Described in 2006 as reporting patient experience (symptoms and quality of life) using a systematic method to complete cancer clinical assessment, diagnosis, and treatment planning.

- Loaded four validated survey instruments (Symptom Distress Scale, EORTC-QLQ-C30, Pain and Discomfort scale, Patient Health Questionnaire-9 depression scale).

- Administered at two time points (baseline and 4-6 weeks post treatment) to increase discussion of patient-reported cancer symptoms and quality-of-life issues with clinical staff.

- **Validity:** RCT of 660 patients with any cancer diagnosis resulting in a nearly 29% increase in the odds of the symptom or quality of life issue being discussed (Berry et al., 2011).

- Further multicenter multivariable analyses suggest a sensitivity to age, with the benefit of assessment strongest in those age >50 years (Berry et al., 2014).

FLIC

- Developed in 1984 to determine the response of cancer patients to their illness and treatment intended for inpatients and outpatients with diagnosed malignant cancer.
- Contains Biological, Psychological, and Social Domains.
- Delivered as a self-administered questionnaire.
- **Validity (Quantitative):** can discriminate significantly between patients in the hospital, getting active treatment, getting adjuvant therapy, off treatment, and receiving follow-up observation and is sensitive to the adverse effects of chemotherapy.
- The FLIC is correlated with the Beck Depression Inventory (0.72), General Health Questionnaire (0.77), Karnofsky Scale (0.69), McGill Pain Questionnaire (0.59), Katz Index of ADL (0.31), and Functional Assessment of Cancer Therapy scale (0.58-0.75) (Schipper et al., 1984).

Voting Question #2

- Considering all PRO assessments in question 1 with greater than or equal to score 2.5, please vote whether or not those PRO assessments combined have available supporting evidence on each of the following desired characteristics:

	Characteristics	Tools (yes/no)
A	Breadth of measures in emotional, social, and physical well-being	
B	Quick throughput to apply to clinical study	
C	Transferable to community practice settings	
D	Measures are not sensitive to differences in age	
E	Measures are not sensitive to line of therapy	
F	Measures are not sensitive to comorbidities	
G	Measures are generalizable to study of combinations of therapies	
H	Used in net benefit analysis based on symptom burden and well-being	

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

Hans Wildiers, Murielle Mauer, Athanasios Pallis, Andrea Luciani, Giuseppe Curigliano, Martine Extermann, and Ulrich Wedding, European Organisation for Research and Treatment of Cancer, Brussels; Hans

Hans Wildiers, Murielle Mauer, Athanasios Pallis, Arti Hurria, Supriya G. Mohile, Andrea Luciani, Giuseppe Curigliano, Martine Extermann, Stuart M. Lichtman, Karla Ballman, Harvey Jay Cohen, Hyman Muss, and Ulrich Wedding

Provides group recommendations for HR-QoL:

- Elderly patients are less willing to compromise HRQoL.
- Maintenance of function and independence should be a major principle of cancer management in the elderly.
- HRQoL should be primary endpoint or part of composite endpoint.

Discussion Questions

- Are there PRO assessments other than those listed in question 1 that have adequately stated evidence-based criteria and processes?
- Are there additional desired characteristics other than those listed in question 2?

Voting Question #3

- How confident are you that each of the following assessment intervals are appropriate measurement periods for a valid PRO assessment?
  a. Variable event-dependent frequency interval (i.e. upon admission and after discharge)
  b. Fixed time-dependent frequency interval (i.e. weekly, monthly, or yearly)

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Confidence ***Intermediate*** ***High Confidence***

Voting Question #4

- How confident are you that a PRO assessment over the course of the following study durations identifies a meaningful durable treatment effect with a valid PRO?
  a. 6 months
  b. 12 months
  c. 24 months

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Confidence — Intermediate — High Confidence

Voting Question #5

- How confident are you that PRO assessments can provide meaningful results when studied with each of the following control populations?
  a. patient him/herself, before and after intervention
  b. usual care versus protocol-driven intervention
  c. historical control

Use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1 — 2 — 3 — 4 — 5
Low Confidence — Intermediate — High Confidence

References Part 1

1. Aaronson et al., for the European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI 1993; 85:365-376.
2. Anderson et al., Symptom burden in patients undergoing autologous stem-cell transplantation. Bone Marrow Transplantation. 2007; 39:759-766.
3. Berry et al., Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. JCO 2011; 29:1029-1035.
4. Berry et al., Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial. JCO 2014; 32:199-205.
5. Cleeland et al., Assessing Symptom Distress in Cancer Patients: The MD Anderson Symptom Inventory. Cancer. 2000; 89(7):1634-1646.
6. Cook et al., PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrate clinical validity across a range of chronic conditions. J Clin Epi. 2016; 73:89-102.
7. DeWalt et al., Evaluation of Item Candidates: The PROMIS Qualitative Item Review. Med Care. 2007; 45 (Suppl1):S12-S21.

References Part 2

8. Dueck et al., Validity and Reliability of the US NCI's PRO-CTCAE. JAMA Oncol. 2015; 1(8):1051-1059.
9. Kotronoulas et al., What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014; 32:1480-1501.
10. Mitchell et al., Validation of the NCI PRO-CTCAE in women receiving treatment for metastatic breast cancer. ASCO Annual Meeting; 2012; Chicago, IL.
11. Rogers et al., The addition of mood and anxiety domains to the university of Washington quality of life scale. Head & Neck. 2002; 24(6):521-529.
12. Rogers et al., The patients' account of outcome following primary surgery for oral and oropharyngeal cancer using a "quality of life" questionnaire. Eur J Cancer Care (Engl) 2008; 17(2):182-188.
13. Rogers et al., Screening for dysfunction to promote multidisciplinary intervention using the University of Washington Quality of Life Questionnaire. Arch Oto Head Neck Surg. 2009; 135(4):369-375.
14. Schipper et al., Measuring the quality of life of cancer patients: the functional living index-cancer: development and validation. JCO. 1984; 5:472-483.