DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000117

David Cella, PhD
Professor and Chair,
Department of Medical Social Sciences
633 North Saint Clair Street, 19th Floor
Chicago, Illinois 60611

Dear Dr Cella:

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000117 received on May 17, 2019 by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for the Network/Function Assessment of Cancer Therapy-Disease Related Symptoms (NFKSI-DRS), a patient-reported outcome (PRO) proposed for the assessment of disease related symptoms in patients aged 18 years or older, who have advanced or metastatic (AJCC stage IV) renal cell carcinoma (RCC).

FDA has completed its review and has agreed to accept your LOI into the CDER COA Qualification Program. FDA's response to the questions included in the LOI and additional comments can be found below:

Question 1: Does the Agency agree that this proposal is a reasonable starting point for a clinical outcome assessment (COA) package?

FDA Response*:* Yes, the agency agrees that the proposed LOI, in principle, is a reasonable starting point for a COA package for RCC. However, we have the following comments:

Your proposed tool, the NFKSI-DRS contains a mix of general symptoms associated with advanced/metastatic cancer (including metastatic RCC), i.e., concepts that could be disease or treatment related (e.g., pain, fatigue and anorexia) and a concept that is more specific to RCC (e.g., blood in urine). FDA notes that in the metastatic stage, symptomatology for patients with RCC tends to shift towards generalized symptoms and that most of the symptom burden is no longer specific to RCC; thus, these RCC-specific symptoms that are currently included may no longer be as relevant.

Because of this, FDA strongly recommends taking a modular approach to the development of NFSKI-DRS. With this approach, the symptoms of pain, fatigue and anorexia are considered general advanced cancer symptoms because they are commonly reported by many patients with advanced/metastatic cancer, including RCC. Disease-specific concerns (such as 'blood in urine' in patients with RCC) can also be explored further in patients with advanced disease and can be moved to the end of the tool. Consider also capturing how much the patient is troubled by blood in urine (if present). The FDA recommends a modular approach because it may provide an opportunity to expand the context of use of your proposed tool, should this tool be applicable to other advanced solid tumor malignancies (e.g. metastatic prostate cancer or breast cancer) that typically do not have symptomatology that is specific to the tumor type in metastatic settings. Because some items may eventually be dropped pending the qualitative and quantitative research (e.g., blood in urine), placing lower priority items last in the order completed by patients is recommended.

We recommend that the disease-related symptom-physical (DRS-P) subscale include only items that reflect the most general symptoms of advanced metastatic cancer patients (i.e., pain, fatigue and anorexia).

The proposed scale includes two items on pain, but patients may have difficulty differentiating between the concepts of pain and bone pain. It may be beneficial to include only the item on pain (i.e., I have pain), as it is more generalizable, and it may be difficult for the patient to differentiate between pain and bone pain.

The NFKSI-DRS includes both positively and negatively worded items. While we recognize that this approach is often used to control for response effects (e.g., acquiescence bias), there is concern that subjects may overlook the change in direction of the item(s). We recommend that all items be worded in a consistent direction (e, g., change the direction of item 11 [I have a good appetite].

To facilitate data interpretation and clearly describe clinical benefit, we recommend that you only include the following 3 items:

- Item 2: I have pain
- Item 4: I feel fatigued
- Item 11: I have a poor appetite

Question 2: Does the Agency agree there is sufficient need for a COA to assess disease-related symptoms among patients with RCC?

FDA Response: See QRT Response to Question 1. There is an unmet need for a fit-for-purpose PRO measure to assess general disease related symptoms associated with advanced/metastatic cancer, including RCC.

Appendix 1 of this letter contains the contents to include in your submission to reach the next milestone (qualification plan). Please contact CDER's COA Qualification Program at

COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #117).

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300170743, cn=Elektra J. Papadopoulos -S
Date: 2019.08.16 15:55:15 -04'00'

Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research

Amna Ibrahim -S

Digitally signed by Amna Ibrahim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984
Date: 2019.08.16 16:05:36 -04'00'

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1 (DOP1)
Office of New Drugs
Center for Drug Evaluation and Research

Appendix 1: COA QUALIFICATION PLAN

The COA Qualification Plan should be accompanied by a cover letter and should include the following completed sections. This plan should contain the results of completed qualitative research and the proposed quantitative research plan. If literature is cited, please cite using the number assigned to the source in a numbered reference list.

Note: Sections 1 and 2 will be posted publicly under Section 507 as well as any appendices or attachments referred to in those sections. Section 507 refers to section 507 of the Federal Food, Drug, and Cosmetic Act [FD&C Act] which was created by Section 3011 of the 21st Century Cures Act.

Section 1: Proposed Plan for COA Qualification

1.1 Introduction and overview

- This should include a concise description of the disease and the clinical trial setting in which the COA would be used, the limitations of existing assessments, a brief description of the existing or planned COA, and the rationale for use in drug development.

1.2 Concept of Interest for meaningful treatment benefit

- Describe the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., the specific symptom and/or sign presence or severity or limitations in performance or daily activities relevant in the targeted context of use).

1.3 Context of Use

- Identify the targeted study population, including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, language/culture groups).
- Identify the targeted study design. Most commonly the COA will be used to assess the change (compared to a control) induced by a medical treatment.
- Identify the targeted study objectives and endpoint positioning (i.e., planned set of primary and secondary endpoints with hierarchy). Usually, the COA will serve as a primary or secondary study endpoint measure.

1.4 Critical details of the measure to the degree known

- Reporter, if applicable

- Item content or description of the measure (for existing instruments, the specific version of the instrument and copy of the tool from which quantitative evidence has been or will be derived)
- Mode of administration (i.e., self-administered, interview-administered)
- Data collection method

1.5 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable (i.e., working group, consortia).

Section 2: Executive Summary

- High-level summary of what is included in the Qualification Plan and results to be described in the sections below

Section 3: Qualitative Evidence and Conceptual Framework

- Evidence of content validity (i.e., documentation that the COA measures the concept of interest in the context of use)

3.1 Literature review
3.2 Expert input
3.3 Reporter input (e.g., for PRO measures, concept elicitation, focus groups, or in-depth qualitative interviews to generate items, select response options, recall period, and finalize item content; for PerfO measures, evidence to support that the tasks being performed are representative of the meaningful health aspect of the concept of interest and are relevant to ability to function in day-to-day life)
3.4 Concept elicitation
3.5 Item generation
3.6 Cognitive interviews
3.7 Draft Conceptual Framework (for existing instruments, the final version conceptual framework)

Sections 4, 5, and 6: Proposed Quantitative Analysis Plan

Section 4: Cross-sectional evaluation of measurement properties

4.1 Item Level Description

4.1.1 Item descriptive statistics including frequency distribution of both item response and overall scores, floor and ceiling effect, and percentage of missing response
4.1.2 Inter-item relationships and dimensionality analysis (e.g., factor analysis or principal component analysis and evaluation of conceptual framework)
4.1.3 Item inclusion and reduction decision, identification of subscales (if any), and modification to conceptual framework

4.2 Preliminary scoring algorithm (e.g., include information about evaluation of measurement model assumptions, applicable goodness-of-fit statistics). The scoring algorithm should also include how missing data will be handled.

4.3 Reliability

- 4.3.1 Test-retest (e.g., intraclass correlation coefficient)
- 4.3.2 Internal consistency (e.g., Cronbach's alpha)
- 4.3.3 Inter-rater (e.g., kappa coefficient)

4.4 Construct validity

- 4.4.1 Convergent and discriminant validity (e.g., association with other instruments assessing similar concepts)
- 4.4.2 Known groups validity (e.g., difference in scores between subgroups of subjects with known status)

4.5 Score reliability in the presence of missing item-level and if applicable scale-level data
4.6 Copy of instrument
4.7 User manual and plans for further revision and refinement

- 4.7.1 Administration procedures
- 4.7.2 Training administration
- 4.7.3 Scoring and interpretation procedures

Section 5: Longitudinal evaluation of measurement properties (If Known)

5.1 Ability to detect change

Section 6: Interpretation of Score (If Known)

6.1 Evaluation and definition of meaningful within person change (improvement and worsening)

Section 7: Language translation and cultural adaptation (If Applicable)

7.1 Process for simultaneous development of versions in multiple languages or cultures
7.2 Process of translation/adaptation of original version
7.3 Evidence that content validity is similar for versions in multiple languages

Section 8: Questions to CDER

Section 9: References

- References and copies of the most important references that the submitter feels CDER reviewers may want to review.

Section 10: Appendices and Attachments

- Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s))