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October 15, 2018

The Honorable Scott Gottlieb, MD  
Commissioner, Food and Drug Administration  
Dockets Management Staff (HFA-305)  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: FDA Standard Core Clinical Outcome Assessments and Endpoints (Notice No. NOT-FD-18-014)

Dear Commissioner Gottlieb:

On behalf of the Celiac Disease Foundation, I am writing in support of the submitted comments of the National Health Council (NHC) on the Food and Drug Administration's (FDA) Request for Information (RFI) related to Standard Core Clinical Outcome Assessments and Endpoints. I have attached a brief note of support and the NHC comment letter. Thank you.

The Celiac Disease Foundation is the nation's leading disease advocacy organization for celiac disease and non-celiac gluten/wheat sensitivity. We accelerate diagnosis, treatments, and a cure through research, education, and advocacy to improve the quality of life for all those affected.

We appreciate the opportunity to respond to the RFI and we write to support the NHC's general recommendations on the RFI and specific answers to questions listed in the RFI.

Sincerely,



James J. Watson  
Chairman of the Board



Marilyn G. Geller  
Chief Executive Officer

Celiac Disease Foundation is a 501(c)3 nonprofit organization. Contributions to the organization are tax-deductible under IRS code 170(s), Tax ID#95-4310830. If you have questions, please call 818.716.1513, x101



# National Health Council

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The Honorable Scott Gottlieb, MD  
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5630 Fishers Lane, Rm. 1061  
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Re: FDA Standard Core Clinical Outcome Assessments and Endpoints (Notice No. NOT-FD-18-014)

Dear Commissioner Gottlieb:

The National Health Council (NHC) is pleased to provide comments on the Food and Drug Administration's (FDA) Request for Information (RFI) related to Standard Core Clinical Outcome Assessments and Endpoints.

The (NHC) is the only organization that brings together all segments of the health community to provide a united voice for the more than 160 million people with chronic diseases and disabilities and their family caregivers. Made up of more than 120 diverse national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include professional and membership associations; nonprofit organizations with an interest in health; and representatives from the pharmaceutical, generic drug, health insurance, device, and biotechnology industries.

The NHC supports the FDA's interest in promoting the "development of publicly available, standard core sets of Clinical Outcome Assessment (COA) measures for specific disease indications." We appreciate the amount of consideration required to develop the RFI's thought-provoking questions. Our comments in section one offer general recommendations on the RFI, and section two provides specific answers to questions listed in the RFI.

## I. Overarching Comments

### Patients must be involved in a multi-stakeholder approach.

Patients and their family caregivers need to have a prominent role to inform this work to ensure the assessments and endpoints being measured are important to patients. In addition to COA measures, others such as biomarkers, clinical, morbidity or mortality measures may also be very important to patients. While these may not fall into a core set of COA measures, it is also important that they are incorporated and weighted consistently into trials to facilitate downstream patient and clinician decision-making.

To date, patient involvement in core outcome set (COS) development has been limited. Several examples of patient collaboration in COS development have been published.<sup>1</sup> However, the term COS is used ambiguously. Sometimes referring to a set of outcomes only, other times referring to both outcomes and corresponding outcome measures. It is imperative that FDA's initiative promotes patient centrality in both development of broad core outcome sets, as well as including only patient-centered measures as core clinical outcome assessment and endpoint sets (CCOASES) in COSs.

Past, current, and future work on Patient-focused Drug Development (PFDD) should be aligned with and incorporated into core outcome set development. For example, 'Voice of the Patient' reports emerging from both FDA- and externally-led PFDD meetings describe patient perspectives on disease symptoms, daily impacts that matter most and current approaches to treatments. COSs should be developed in a multi-stakeholder fashion, including patients, patient organizations, caregivers, health care providers, industry, payers, value assessors, etc. with meaningful patient engagement as the driving force. When properly developed and operationalized through a transparent process this results in efficiencies in drug development as well as downstream in the health care delivery ecosystem.

Moving forward, one challenge for patient groups interested in participating in COS development is the lack of patient-specific training; as FDA seeks to develop CCOAES, patient-specific training will also be needed. Additionally, pay firewalls for access to peer-reviewed journals prevent many stakeholders around the world, in particular patient groups in the United States, from learning about the validity of existing measures. It is important that data on the development and validation of measures is made publicly available and is easily locatable.

*FDA should clearly define terms and differentiate between them.*

It is important for FDA to clearly define, differentiate, and articulate overlap between terminology, including "core outcome sets" (COSs) and "core clinical outcome assessment and endpoint sets" (CCOAESs). We offer our interpretation of these terms in Appendix I. Importantly, CCOASES should only include patient-centered outcome measures. Understanding the dichotomy between patient-centered outcomes and not patient-centered outcomes is critical. To get to patient-centered outcomes and endpoints, patients must be the driving force behind what outcomes are deemed important. If COA measure developers adhere to FDA's Roadmap and Patient-Reported Outcome (PRO) guidance, the resulting measures should be patient-centered.

*FDA should develop a stepwise approach to identify outcomes and then measures*

The NHC recommends that FDA first identifies the outcomes that matter to patients with a specific disease indication. For example, it would be reasonable to define an outcome set that should be considered for all diseases, e.g., (1) symptoms, patient-reported signs, and decrements in daily functioning that define disease/condition severity from the patient perspective, (2) clinician assessment of severity, (3) patient preference for treatment alternatives, (4) patient global item of severity, (5) clinician global item of severity, (6) disease-specific impact on quality of life. Once a set of patient-prioritized outcomes has been developed, a corresponding set of patient-centered "measures, tools, and endpoints" can be identified.

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<sup>1</sup> de Wit M, Abma TKoelewijn-van Loon M, et al. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences BMJ Open 2013;3:e002241. doi: 10.1136/bmjopen-2012-002241

## II. Responses to Questions in the RFI

*#1. If currently available measures do not fit the topics, concepts, or wording patients identified for a given disease area based on recent patient input—for example the words or time frame used to describe fatigue or pain may be different than wording in available measures—how would you efficiently address this?*

Candidate legacy measures should be evaluated for entry into a core COA measure set. Only measures consistent with the goals for the core outcome set – including patient centricity and documentation of appropriate measure development and validation – should be considered eligible for entry into a measure set. For the evaluation of patient centricity, the existing measure pedigree should be examined to determine if the outcomes/concept(s) of interest, words used, and other aspects compatible with what is known from existing patient experience data (patient provided information). It should be vetted by the patient community through methods identified in the FDA final/draft guidances<sup>2</sup> on gathering patient experience data. The language used in the core set should be aligned with what patient have identified as the words, terms, and expressions they use. Additionally, new administrative modes, such as electronic versions of paper-based instruments must be validated prior to inclusion in a COA measure set.<sup>3</sup>

If it is determined the measure is not patient centered, the measure would need to be modified using methods described in the forthcoming guidances<sup>3</sup> on PFDD to modify the measure. The modifier of the measure must determine whether new qualitative and quantitative research is needed based on the of divergence of the original legacy measure and the desired concept of interest (based on patient-experience data) and context of use. Some measures may require small modifications (e.g., the concept addressed is one that is important but a change from a clinical term to a patient-friendly term is required). Some may require extensive modifications (e.g., important concepts are missing, or, of several concepts addressed, only one is relevant; words and phrases need to be changed; some items are poorly understood). Measure developers should document which modifications were made, methods used, and rationale for changes.

FDA's Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Different COA Measures<sup>3</sup> provides limited language on instrument modification. However, professional organizations such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Quality of Life Research (ISOQOL) have published methodological guidance and examples of instruments that have been adapted or modified. While useful methodological resources, these reports do not specifically consider instrument modification to improve patient centricity.<sup>4,5,6</sup> All stakeholders would benefit if the FDA was able to provide case examples of instrument modifications that are specific to addressing patient centricity.

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<sup>2</sup> Food and Drug Administration. FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. Accessed from <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm610279.htm>

<sup>3</sup> Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims <https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf>

<sup>4</sup> Powers III, JH, Patrick DL, Walton MK, et al. Clinician-Reported Outcome (ClinRO) Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. Value Health 2017; 20(1):2-14.

<sup>5</sup> Walton MK, Powers JA, Hobart J, et al. Clinical outcome assessments: A conceptual foundation – Report of the ISPOR Clinical Outcomes Assessment Emerging Good Practices Task Force. Value Health 2015; 18:741-52.

<sup>6</sup> ISPOR. Good Practices for Outcomes Research Reports: Patient-centered Research. <https://www.ispor.org/heor-resources/good-practices-for-outcomes-research/report/-in-category/categories/patient-centered-research>

*#5. For a given disease area, what approaches can be taken to engage multiple authorities (e.g. international regulatory bodies, HTAs) and other decision makers (e.g., professional societies, research organizations, clinicians, regulated medical product industry) to gain needed input and ultimate acceptance of the same standard core set—while minimizes overall reporting burden for patients living with that disease?*

We recommend that FDA adopts or adapts practices that have already been implemented for other research. For example, the Center for Medical Technology Policy's (CMTP) Green Park Collaborative (GPC), a multi-stakeholder forum that includes participants located within the United States and abroad, including international HTAs. CMTP has also been involved in core outcome set development. The Critical Path Institute successfully convenes regulatory agencies, industry, and academia through its Patient-Reported Outcome Consortium. The Duke-Margolis Center for Health Policy frequently convenes interdisciplinary working groups for its health policy research. It is important that existing processes are reviewed to ensure that they are as efficient as possible. Consideration should be given regarding how patients can benefit from this work even while metrics continue to evolve.

To ensure the patient-centricity of core sets, governance structures should be established to ensure that patient perspectives are emphasized. While it is critical that disease-specific experts and patients are involved in core outcome set measure development, in some cases, it may make more sense for umbrella organizations to represent large stakeholder groups, particularly as efforts become more international. For example, it may be more practical to engage the International Network of Agencies for Health Technology Assessment (INAHTA) or European Network for Health Technology Assessment (EUnetHTA) instead of individual HTAs. Patient Focused Medicines Development (PFMD) is an independent coalition of health stakeholders and is experienced at convening stakeholders from around the world on patient engagement. The National Health Council (NHC) frequently convenes patient-led, interdisciplinary working groups for its health policy research and would welcome the opportunity to assist in any way the Agency may deem helpful.

*#6. What if publicly available measures and tools are not as good of a fit compared to a proprietary measure set that is licensed to those able to pay a more-than-nominal fee and accept the terms specified by the license holder—how would you approach this?*

This is an important challenge that will require collaboration with measure developers and possibly a publicly-funded coordinating body. It is important that the best measures are used, but the costs associated with proprietary measures can be exorbitant. Ideally, future measure development should be undertaken in a pre-competitive setting and funded by multiple stakeholders involving patients to reduce challenges associated with licensing. Existing proprietary measures need to demonstrate the same level of scientific rigor and documentation of patient input from the appropriate patient population to ensure that they are targeted to that patient group. When comparing publicly available measures to proprietary measures, weight should be given to those that prioritize patient input.

*#8. For a given context of disease and patient subpopulation:*

*#8a. How would you identify the limitations of existing measures and tools?*

Patient engagement with representative populations is an important tool to identify limitations of existing measures and tools. Start *with the patients* not the measures. Engage with patients to first identify the outcomes/concepts of interest important to them. Then, examine legacy measure evidence to determine if the outcomes/concepts that are captured also align with the patient input.

Transparency of methods used by legacy-measure developers for concept elicitation, cognitive interviewing, psychometric validation, etc., are critical to assess the measure pedigree and identify possible

limitations. Recent research indicates that patient diaries and visual analogue scales may require additional scrutiny due to lack of transparency in development/validation methods.<sup>7</sup> It is likely that for many legacy measures this information will simply not be available. For example, if the concepts of interest in COA measures are not aligned with patient or caregiver input – the measure is clearly insufficient. Direct patient engagement in addition to patient-generated data sources, such as registries, can play a role. Further guidance on developing methodologically rigorous measures, including considerations for rare diseases, have been published by ISPOR and ISOQOL task forces.

*#8b. What sort of limitations would you anticipate may be identified? Please offer some examples based on your previous experience.*

One significant limitation in this space is that many legacy instruments that are still in use were developed without patient and/or caregiver input. These may measure concepts that are either unimportant to patients or ancillary to patient-prioritized concepts. The measure would thus be unusable and not fixable.

Absent or insufficient cognitive debriefing with a diverse group of patients will result in instruments that are not understandable to patients. For example, the terms used to describe symptoms may not be the terms that patients would use to describe those same symptoms resulting in confusion. Specific examples are described in this recent article.<sup>8</sup>

*8c. For the various types of issues identified, what would you do to address these limitations? What has been your experience with the effectiveness of these strategies in the past?*

If the concepts of interest measured by the instruments are those that patients state are important to them, it may be possible to modify instruments through additional validation work. The FDA's PRO guidance, ISPOR, and ISOQOL task force publications describe methods for validating measures. One area the NHC sees as vital is to continue to push for increased transparency of methods used for development. Without transparency, it is difficult for stakeholders to assess limitations in the methods used by measure developers.

*#11. What are the expertise and operation management skill sets needed for the work described in this RFI?*

As discussed in question #5, there are current practices the FDA can look to adopt from organizations with experience facilitating multi-stakeholder initiatives (e.g., NHC, CMTP, Critical Path Institute, Duke-Margolis, PFMD, etc.). These organization must have strong governance structures and promote engagement and contributions from all participating stakeholders, especially patients, such as:

- Patient organizations with familiarity of all relevant patient subgroups
- Professional organizations, including medicine, nursing, pharmacy and other relevant specialties
- Measure developers with expertise in qualitative research, psychometrics
- Biopharmaceutical and medical device development, especially health economics and outcomes research and clinical trial expertise
- Value assessors/Health Technology Assessment bodies
- Insurers
- Employers
- Regulators with experience in COAs; Representatives from the individual review divisions

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<sup>7</sup> Oehrlein EM, Peretto EM, et al. Patient-Reported Outcome Measures in the Food and Drug Administration Pilot Compendium: Meeting Today's Standards for Patient Engagement in Development? Value Health. 2018 Aug;21(8):967-972. doi: 10.1016/j.jval.2018.01.004.

*#14. What steps can reduce patient and other informants' burden?*

This question could refer to patient and other informants' burden in developing a COS/CCOAES or COA measure data collection within the scope of a study. Our feedback pertains to the development of a COS. Understanding how to reduce patients' burden within the scope of a study can be achieved by co-developing research protocols in partnership with patients. Accommodations should be made for patients to participate in COS and CCOAES development remotely, as needed. Patient participants should be compensated for their participation in COS and CCOAES development. It is important for patient organizations to collaborate when collecting data on subgroups within their patient populations. Existing data assets and evidence should be utilized to the extent possible. Processes should be carefully thought out and established before beginning COS measure development to ensure efficient participation. Expectations of patient organizations should be clearly described well in advance of convening stakeholder forums to ensure they are able to collect all data well in advance.

**III. Conclusion**

The NHC fully supports the FDA's focus on promoting "development of publicly available, standard core sets of Clinical Outcome Assessment (COA) measures for specific disease indications." In this letter, the NHC has emphasized that patient-prioritized outcomes should serve as the basis of COSs and CCOAESs. The NHC appreciates and applauds the FDA for recognizing and requesting information on how standard core sets can be improved upon and updated.

Please do not hesitate to contact Eric Gascho, our Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable by phone at 202-973-0545 or via e-mail at [egascho@nhcouncil.org](mailto:egascho@nhcouncil.org).

Sincerely,



Marc Boutin  
Chief Executive Officer  
National Health Council

**Appendix A.**

According to the RFI, CCOAES “would reflect measures, tools, and endpoints that assess a minimum list of impacts that matter most to patients and are likely to demonstrate change relating to disease burden, treatment burden, and, if applicable, physical function.” The Core Outcome Measures in Effectiveness Trials (COMET) initiative defines COS as “an agreed minimum set of outcomes or outcome measures... It is a recommendation of ‘what’ should be measured and reported in all trials in a specific area.” They define a Core Outcome Measurement Instrument Sets (COMISs) as “details on the instruments or tools to use to measure the outcomes in a COS.”<sup>9</sup> COMET’s definition that a COS may refer to outcomes or outcome measures results in ambiguity.

Our interpretation is that a COS is a broad range of possible outcomes identified through multi-stakeholder consensus building. Outcomes comprising a COS may include those that are patient-centered (i.e., identified and prioritized by patients) and not patient-centered (i.e., not prioritized by patients). A COS includes all types of outcomes including, COAs, biomarkers, survival outcomes, etc. A COMIS is an extension of a COS meaning it includes a broad range of measures associated with the COS. A COMIS includes patient-centered and non-patient-centered outcome measures (see Figure 1). A CCOASES is subset of a COMIS and includes only patient-centered outcome measures falling under the COA umbrella: patient-reported outcomes measures (PROMs), clinician-reported outcome measures (ClinRo), observer-reported outcome measures (ObsRO), and performance outcome measures.

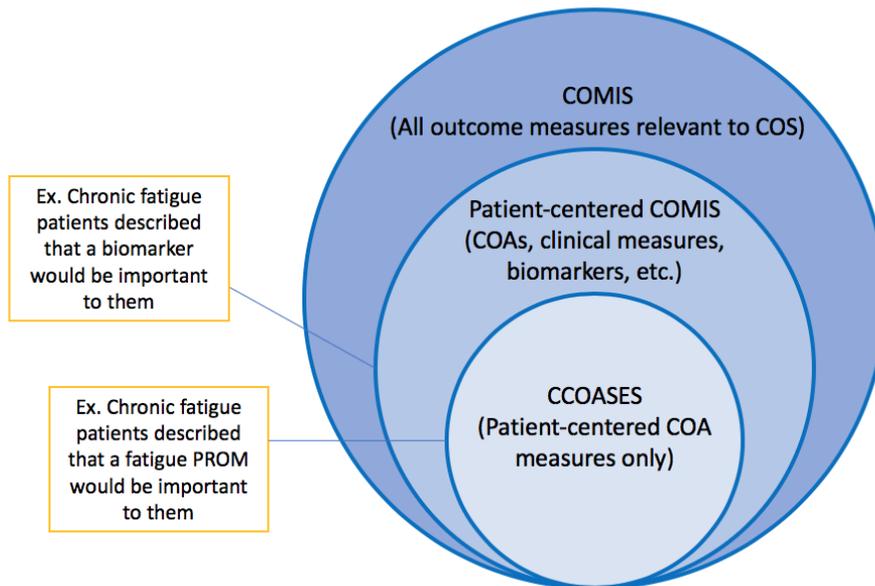


Figure 1. COS vernacular

<sup>9</sup> Core Outcome Measures in Effectiveness Trials. Core Outcome Set (COS) Glossary. <http://www.comet-initiative.org/glossary/cos/>