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Division of Dockets Management (HFA-305)
Food and Drug Administration
U.S. Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023–D–0026 Comments on the Draft FDA Guidance "Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making"

To Whom It May Concern,

The Alliance for Aging Research ("Alliance"), in particular its Talk NERDY program, appreciates the opportunity to review and comment on the draft guidance entitled Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making. The Alliance is the leading nonprofit organization dedicated to accelerating the pace of scientific discoveries and their application to vastly improve the universal human experience of aging and health. The Talk NERDY program provides a specialized learning experience for older adult patient advocates and their caretakers. Talk NERDY educates this population on clinical research: what it is, how it works, and how it is relevant to them. Talk NERDY's goal is to accelerate and improve health care research in the aging population.

Talk NERDY and the Alliance actively support the FDA's creation of the Patient-Focused Drug Development Series and agrees that a systematic approach is integral to ensuring that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. Development processes that include substantive patient input on the research process, study format, endpoints assessed (including clinical outcomes assessments), and clinical meaningfulness, have been shown to provide methodological benefits (more appropriate wording and timing of research instruments and interventions, increased readability and accessibility of research materials, and **more relevant research outcomes/endpoints)**. Study quality benefits include improved recruitment and retention, improved trial experience/satisfaction by study participants, more adherence to research

protocols and faster study completion.[1]

Comments on the draft Guidance are listed below by section and line number.

B. Purpose and Scope of PFDD Guidance 4

Lines 69-70: Talk NERDY agrees with the statement "it is important to understand how the COA-based endpoint corresponds to changes relevant to patients (e.g., the type and extent of change that is meaningful to patients) and strongly encourages early interactions with patients in the development of COA-based endpoints to ensure that the patient and the clinical research staff have the same understanding of "meaningful."

II. COA-BASED ENDPOINT CONSIDERATIONS

1. Selecting and Justifying Endpoints

Lines 118-119: Talk NERDY agrees with these statements but suggests that FDA also ask sponsors to consider the sustainability of an inference of treatment effect under Real World Evidence (RWE).

Lines 168-173: Talk NERDY strongly encourages FDA to consider emphasizing primary data collection for the support of endpoints with literature reviews as a backup. Involving the patients early in the process is integral to developing clinical trials that accrue, answer questions relevant to the target population, and result in interventions that will be utilized by that population in the real world.

a. Considerations for baseline administration of COAs relevant to COA-192 based endpoints

Line 205: Talk NERDY suggests the replacement of the word severity with measurable. The

[1] Lidewij Eva Vat , Teresa Finlay , Tjerk Jan Schuitmaker-Warnaar , Nick Fahy , Paul Robinson , Mathieu Boudes , Ana Diaz , Elisa Ferrer , Virginie Hivert , Gabor Purman, et al. 2020. Evaluating the "return on patient engagement initiatives" in medicines research and development: A literature review. Health Expect. 2020 Feb; 23(1): 5–18.

meaning of severity is open to interpretation, and can be variable, such as in the use of the pain scale.

b. Endpoints constructed by dichotomizing COA scores

Lines 255-260: Talk NERDY strongly agrees with the statement "meaningfully different", but respectfully asks FDA to define meaningfully. Narrative from the sponsor within the IND of the relevance of data used to derive a score threshold and how that does and does not relate to efficacy is strongly encouraged.

e. Endpoint strategies when a disease affects multiple aspects of feeling and functioning

Lines 327-334: Talk NERDY appreciates the inclusion of challenging diseases with multiple aspects of health feeling and functioning that need to be considered for construction of multiple endpoints.

Construct a Multiple Endpoint

Lines 399-405 and 425-428: Talk NERDY respectfully notes that the absence of all symptoms may be possible but is potentially open to bias and therefore may lack reliability. Reporting of symptoms for chronic diseases varies over time and can be quite subjective. Talk NERDY asks that FDA be clear to the sponsor that this is widely variable, dependent on the specific disease in question, and needs to be taken into account when constructing endpoints for challenging, chronic diseases.

Lines 444-448: Talk NERDY strongly recommends involving patients in the initial discussion of multi-component endpoints that clinicians and researchers view as similar. In our experience, that is often not the case for individuals living with the disease and we have also found that often it is surprising to clinicians and researchers who are designing the trials. The Alliance would like to see specific IND requirements for justification vs. general guidance that it should be included.

Lines 470-471: Talk NERDY respectfully asks for greater clarification from FDA on this. How is this possible for multiple component endpoints? What if there is improvement in one

component but a worsened condition in another? It seems this assumes not only that they are symmetric but also have a direct causality/relationship. Perhaps a graphic would be helpful.

Construct a Personalized Endpoint

Lines 480-485: Talk NERDY respectfully asks for greater clarification on the use of this terminology; "most bothersome" versus "most severe" is not clear. The term "bothersome" comes across as patient-speak and "severe" as clinician-speak.

Lines 520-521: What is FDA's expectation for how the trial sponsor accounts for this? How likely is it that this is a result of the trial intervention vs. external factors? See comment above for lines 480-485.

Lines 524-525: Talk NERDY would like to see FDA rephrase this to put the onus on the sponsor to do sufficient data collection with the involvement of patient's affected by the disease in the trial design so that instances of this are rare and/or covered by well-reasoned exclusion criteria.

3. Clinical Trial Duration and Timing of Assessments for COA-Based Endpoints

Lines 552-557: Talk NERDY respectfully asks FDA to clarify that "patient burden" needs to be determined by patients, not by clinical or research staff. See Lines 562-567 below.

Lines 562-567: Talk NERDY agrees with this statement, but respectfully asks FDA to consider changing "might consider seeking" to "should seek" input from members of the patient community. Addressing practical considerations in trial design increases accrual, minimizes drop-out rates, and improves the quality of the data by increasing adherence by participants.

Lines 667-678: Talk NERDY would like FDA to include reference to contacting the appropriate person in the best method for eliciting a response which should be discussed and agreed to prior to commencing the study. Talk NERDY has noted that communication preferences need to be respected and utilized to ensure maximum participation and adherence.

Lines 702-704: Talk NERDY recommends including a request in this section to address what

data is collected, and how, to arrive at that measurement.

Lines 705-706: Talk NERDY strongly supports this statement and encourages FDA to word this statement more strongly than "it would be helpful", such as "it is important to know."

2. How Simple or Familiar is the COA's Metric?

Lines 741-743: Talk NERDY feels it is important to note that one patient's "mild" pain score might be another's "moderate"; so familiarity may help with individual assessments, but caution should be used when assessing across patients.

7. Minimizing Participant Burden

Lines 1458-1459: Talk NERDY strongly agrees with this section in its entirety and recommends that FDA put this section earlier in the document, as the points raised here are relevant to many sections that come before it.

Contact Information

The Alliance's Talk NERDY Program thanks FDA for the opportunity to comment on this guidance. If you have any questions or would like to follow up on the items discussed in our comments, please contact Beth Mathews-Bradshaw, Vice President for Patient Engagement and Research, at bmbradshaw@agingresearch.org. Talk NERDY looks forward to continuing to work with and support the FDA's Patient-Focused Drug Development efforts.

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