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DiMe response to Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5360 Fishers Lane, Rm 1061
Rockville MD 20852

RE: Docket No. FDA-2023-D-0026-0002:

The Digital Medicine Society (DiMe) is pleased to respond to the Food and Drug Administration's (FDA) request for comments regarding the Patient Focussed Drug Development Guidance 4: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making.

DiMe welcomes the additional clarity the draft regulatory guidance on Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making seeks to provide. The DiMe response to this guidance will focus on elements that are necessary for additional consideration when considering electronic clinical outcomes assessments (eCOA). In DiMe's Glossary of terms, an eCOA is defined in the following manner:

"A COA describes or reflects how an individual feels, functions, or survives; When a COA is collected using sensor technology, it is called an electronic outcome assessment or 'eCOA'."

Although not directly incorporated into this definition, DiMe's response to the Guidance can also apply to other electronic modes of administration which collect intensive longitudinal data (such as ecological momentary assessment and daily electronic diary assessment).

General comments

Highlight the relevance to eCOA early

DiMe was pleased to see that the Agency highlights the use of eCOAs in medical product development at the end of the guidance, (line 1511 onwards). To further support the implementation of eCOAs within clinical trials, DiMe recommends that an additional statement is made early in the document to underscore that the considerations present in the guidance may also apply to eCOAs, but that additional

considerations may also be warranted. This would augment the use of eCOA examples already included in the guidance (e.g. line 145)

Specific comments

Accounting for eCOAs in the Baseline period

In line 198, the Agency rightly suggests that some COA measurement strategy designs necessitate longer recording during the baseline period. DiMe believes that it is important to offer an example of an eCOA where a baseline recording period should include multiple days or weeks of assessment in order to account for day-to-day variability. Similar examples can be made for eCOAs for the next bullet point in this section on line 201.

Handling intensive longitudinal data to assess trial endpoints

In section 2b (starting line 215), the Agency mentions the use of fixed COA scores at a given time point or the use of summary scores over a predetermined time point. We commend the Agency on noting that repeated measures (which are of particular relevance to eCOAs) can be accounted for as part of a repeated measures model. However, it is not clear whether the Agency intends that the use of these models applies to endpoint assessment, or whether the Agency is suggesting that these models should be used to derive individual patient level summary COA scores to be used as part of a further analysis in a two-step procedure.

Using all available data in a model, rather than using a summary score such as an average over a given time period, is an appropriate way to handle intensive longitudinal data. When summary statistics are used in a model intending to test an endpoint, information (such as the variance underlying the summary score) is hidden from this model. It is imperative that the Agency makes this point clear for the use of any procedure using intensive longitudinal data, in order for the field to make informed choices about the analysis type the Agency would expect to see proposed. Making these statements early will allow interactions with the Agency to start from a more mature point, and speed up the overall drug development process.

Timing of assessments for eCOA-based endpoints

DiMe appreciates the considerations the Agency has made regarding the assessment timings. It would be beneficial for the research community to have this section expanded to account for the frequency of eCOA assessments relative to visit cycles. For example, a wearable sensor-based eCOA is able to collect data daily. However, if

the sponsor is only interested in assessing change from baseline to a specific time point(s), then it is unnecessarily burdensome to collect data everyday. However, the amount of time preceding each visit that the eCOA data is collected is important and will depend on 1) the variability inherent in the construct under investigation for the specific disease or condition and 2) any expected period or cyclical pattern that occurs. One example of the latter point could be that people tend to be more active on the weekend than on weekdays. It could be important that a measurement strategy is developed to collect data on both weekend days and weekdays in the critical window (where qualitative patient interview or observational data supports this notion).

Clarifying whether the Agency intends meaningful score differences (MSD) to be an individual-level or group-level metric

In section 2c (starting on line 242), the Agency rightly states that dichotomisation of continuous or categorical scores leads to a loss of power and that analyzing the data in the original metric may be preferable. The Agency also states on line 266 that it is possible to assess the interpretability of continuous outcomes in Section III.

To this effect, the Agency introduced meaningful score differences as a concept (MSD; line 773). MSD is initially stated to reflect a meaningful within-patient change (line 776), but later is suggested that MSD can be used to interpret group level mean:

"Regardless of the approach used to determine the MSD, the MSD can be used in at least two ways: (1) to evaluate the expected treatment effect for the average patient in some target population; or (2) to use as a threshold in descriptive analyses that identify individual patients who might have changed by a meaningful amount. Both of these applications will be discussed (see III.C) following a review of approaches for selecting a value or range of values for MSD."

The methods and the use of the MSD seem to be conflicting. MSD seems to relate to the interpretation of either *within-patient change*, or to interpreting the resulting endpoints relying on the assessments of *group-level* change using continuous data. Individual level within-patient change thresholds often necessitate a dichotomised endpoint measure assessment (such as responder analysis, time-to-event, etc). This is because the patient either achieves this threshold or does not, and therefore we are in the business of assessing proportions. On the other hand, group-level thresholds are used to assess whether the mean difference in change between a treatment group and a comparator is meaningfully different. It is important that the Agency is clear on the use of the MSD at *each of* the within-patient, within-group and

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between-group levels in order for sponsors to be able to interpret the results arising from the assessment endpoints based on continuous data. It is impossible for a single method (and resulting thresholds arising from that method) to be robustly applicable to each of these scenarios.

We thank the FDA for allowing the opportunity to comment on incorporating clinical outcome assessments into endpoints for regulatory decision-making.