DRUG DEVELOPMENT TOOL
QUALIFICATION PLAN DETERMINATION
DDT COA #000053

Lynn Hudson, PhD
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Critical Path Institute
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Tucson, AZ 85718-5893

Dear Dr. Hudson:

We have completed our review of the Qualification Plan (QP) for Drug Development Tool (DDT) COA #000053 received on October 10, 2019, by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The QP is for the Symbol Digit Modalities Test (SDMT), a performance outcome assessment, proposed for the assessment of cognitive disability in adults with a diagnosis of MS and a relapsing clinical course, to include relapsing remitting MS (RRMS) and active secondary progressive MS (active SPMS).

FDA has completed its review and has agreed to accept your QP. FDA's response to the questions in the QP and recommendations for the Full Qualification Package (FQP) are below.

Question 1: Based upon the data that will be presented from the literature review and the analyses of SDMT results from studies in RRMS patients, does the QRT support the Qualification Plan of SDMT for use in the COU target population of RRMS?

FDA Response to Question 1:
We agree that the proposed QP, in principle, appears reasonable. However, we have identified several issues that will need to be clarified in your FQP.

1. **We have the following request for clarification regarding the scoring algorithm. Page 56 of the QP and the User Manual in Appendix 10.5 state that the first 10 boxes of the SDMT reflect the learning phase and are not included in the SDMT score. However, page 14 of the QP states that the test consists of 120 abstract symbols and that the number of correct responses represents the test result. Please ensure that SDMT scoring in the Full Qualification Package (FQP) is described consistently to clarify this issue.**

2. **We have the following requests regarding the user manual, which you should provide in the FQP:**
    a. **Please submit the user manual for the SDMT in its entirety.**
    b. **Please clarify whether the SDMT user manual was provided to investigators in the ADVANCE and STRATA studies and, if so, please clarify whether the user manual is the same as the one you plan to submit as requested above.**
    c. **Please clarify whether training on administration of the SDMT was provided to investigators in the ADVANCE and STRATA studies and, if so, submit a description of any methods and/or training materials. If this material is located in a document described in the Letters of Authorization, or in previously submitted material, please provide direction to where it can be found.**

3. **Additionally, please clarify in the FQP whether you are seeking qualification for only the oral or written version or for both the oral and written versions.**

Question 2:
MSOAC acknowledges that the MSOAC dataset does not include patients with active SPMS who were tested with SDMT. However, MSOAC will present data from the literature review on the similarity of results from SDMT in all stages of MS. MSOAC will also reference recent regulatory decisions to include active SPMS in drug product labels for drugs that treat relapsing forms of MS. Based upon this information, does the QRT support the qualification of SDMT for use in the COU target population of patients with active SPMS?

FDA Response to Question 2:
Provided that the outstanding items identified in this letter are addressed in your FQP, we support submission of the FQP for the SDMT as a measure of processing speed in relapsing forms of MS, including RRMS and SPMS. Please note that if the SDMT is qualified, the qualification statement will reflect the strength of the evidence described in the FQP.

Additional Comments
Sections 4.2.2-4.2.3 describe how you will handle missing data. The FQP should also include an assessment of missing data (i.e., the magnitude of missing data from the dataset and characteristics of patients with missing data including disease duration and visual impairment, if known).

The following weblink contains the contents to include in your submission to reach the next milestone (FQP): www.fda.gov/media/128005/download. We refer to the QRT Comments letter dated January 28, 2019, regarding formatting of the FQP. Additionally, we refer to our previous requests as described below.

Date requested (document)	Requested Information
• March 7, 2020 (Email from Dr. Papadopoulos to Dr. Robbins)	1. Letters of Authorization to provide access and location to patient-level data in the STRATA and ADVANCE studies
• January 28, 2019 (FDA Comments)	1. MSOAC Dataset 2. Data dictionaries for the datasets (MSOAC and Biogen datasets) 3. Programming code (SAS) used for the MSOAC dataset analysis

Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000053).

Sincerely,

Elektra J. Papadopoulos -S

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Nicholas Kozauer -S

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