DDT #000099 **REQUEST FOR INITIAL BRIEFING PACKAGE**

June 9, 2017

Stephen Joel Coons, Ph.D.,
Executive Director, PRO Consortiumaq
Critical Path Institute
1730 E. River Road, Suite 20
Tucson, AZ 85718-5893
Email: sjcoons@c-path.org

Dear Dr. Coons:

We have completed our review of the Letter of Intent (LOI) submission for DDT COA #000099 dated December 2, 2016, and received on December 6, 2016, by the Clinical Outcome Assessments (COA) Qualification Program. You have proposed the development of a tool to assess severity of asthma signs and symptoms in pediatric asthma patients ages 4-11 using the Child Asthma Diary (CAD).

We agree to enter this project into the CDER COA DDT qualification program. Please prepare an initial briefing package (IBP) that outlines your next steps. The attached Appendix 1 describes the summary information that we suggest be the focus of the initial briefing package. Specifically, it will be important to describe the hypothesized elements you anticipate will be included in the COA e.g., concept of interest for meaningful treatment benefit, item generation), proposed respondents (i.e., patient, clinician, or other observer), and how the components of the COA will be used separately or together to produce a total score (i.e., hypothesized conceptual framework), and how scores will be used to quantify treatment differences between trial groups. Following your next submission, we suggest having a teleconference to discuss the submission and provide additional consultation and advice.

The following are general comments related to the specific questions submitted in your LOI:

1. The Pediatric Asthma WG would like to be able to derive a common endpoint across all ages – from pediatric to adult – in clinical trials but doing so will be a challenge. Is this, from FDA's perspective, an important goal to pursue?
    a) If so, would it require assessment of the same symptoms across the age continuum?
    b) If a common total symptom score is not possible, would domain-specific endpoints be acceptable to bridge across the age range?

ORT Response:

In general, to determine if a common endpoint across pediatric and adult population is appropriate, to the extent possible, evidence should be provided to support that the disease definition and the symptom experience is similar across the population. Also, understanding what the clinical trial objectives and design are for each population and whether a common endpoint is needed should also be explored. As you continue your development work in the pediatric population, a more substantive response to this question may be able to be provided.

2. Would the QRT consider qualifying a hybrid measure that is completed by a parent and child together, in the morning after the child wakes up and in the evening before the child goes to bed? Titration could adjust for the child's age (e.g., parents would complete more questions for children under 8 years.)

   ORT Response:

   If the intent of designing a hybrid PRO/ObsRO is to gather information from both the patient and caregiver perspective, it would still be best to administer separate PRO and ObsRO instruments to capture symptom experiences and observable signs of pediatric asthma, separately.

   a) **We recommend that if you proceed with developing an interviewer-administered option, that you draft training materials to ensure that caregivers are instructed and trained not to influence the child's answers in any way, and that the administration mode (interviewer versus self) for each child remains consistent by age group throughout the entire study.**
   b) **We recommend that you include a check box by every interviewer administered item that asks caregivers to indicate whether or not the child needed their help in answering the item. This would aid in providing data on what age children can consistently complete an interviewer-administered PRO symptom diary without clarification of the items or response options from the caregiver.**
   c) **An interview format is not necessary for older children who can read, write and comprehend on their own. A PRO would be more suitable to reduce overall bias from external influences. We recommend that you conduct additional qualitative interviews to explore the youngest age at which a child can provide reliable and valid self-report of their symptoms. Additionally, we recommend that you consider exploring the use of an interactive PRO that can be administered among younger children, allowing them to hear questions and response options read aloud upon tapping a touchscreen.**

3. Is the FDA aware of any other hybrid measures for pediatric assessment accepted in other therapeutic areas that the Working Group could look into further?

   ORT Response:

   We are currently unaware of any hybrid measures for pediatric assessment.

4. Are there any studies involving wearables to assess frequency of nighttime awakenings in pediatric populations (e.g., wrist band, shirt, flexible patch) that FDA is aware of and can share that could be looked at by the Working Group?

   ORT Response:

   We are currently unaware of any studies that can be offered as examples. Actigraphy could be a useful measure of sleep disturbance among children. It should be noted that actigraphy may have

poor specificity to detect wakefulness after sleep among pediatric patients[1]. Therefore, it will be important to first determine which "sleep performance" variables are most relevant for measuring treatment benefit in your target population (e.g., "sleep latency," "wake time after sleep onset," "total sleep time," "sleep efficiency") and then determine what would constitute a clinically meaningful change in that measurement.

- **Actigraphy systems should be validated in the target population; therefore, a device would have to be appropriately validated in pediatric patients. If a validated device is not available, a standalone validation study would need to be performed.**
- **Decision rules regarding how data will be processed and analyzed will also need to be established; a detailed scoring algorithm or wake threshold sensitivity level would need to be provided for Agency review.**

5. Does FDA have any other suggestions for how to address the challenge of symptom assessment in children who are too young to report for themselves (age 4-7) but whose symptoms are not reliably observable?

ORT Response:

As indicated in our response to Question 2c above, we recommend that you consider exploring the use of an interactive PRO that can be administered among younger children, allowing them to hear questions and response options read aloud upon tapping a touchscreen. You can also explore the potential for an interviewer administered PRO that incorporates methods commonly used in developmental psychology and early childhood education (e.g., pictures or other manipulative exercises like card sorting, figurines, play doh) to aid in eliciting responses from younger children. We encourage you to consider consulting with external experts to gain insight into innovative approaches and best practices for data collection among children ages 4-7.

Additional comments:

If you have any questions, please contact the COA Staff via email at COADDTQualification@fda.hhs.gov. Please refer to DDT #000099.

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
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Date: 2017.06.09 10:46:26 -04'00'

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

Lydia I. Gilbert-Mcclain -S

Digitally signed by Lydia I. Gilbert-Mcclain -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300142798, cn=Lydia I. Gilbert- Mcclain -S
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Lydia Gilbert McClain, MD
Deputy Director
Division of Pulmonary, Allergy and Rheumatology
Office of New Drugs
Center for Drug Evaluation and Research

[1] Meltzer LJ, Montgomery-Downs HE, Insana SP, Walsh CM. Use of actigraphy for assessment in pediatric sleep research. *Sleep Med Rev*. 2012;16(5):463-75.

Appendix 1: Initial Briefing Package Description

CLINICAL OUTCOME ASSESSMENT (COA) QUALIFICATION INITIAL BRIEFING PACKAGE

The COA qualification initial briefing package (IBP) should be accompanied by a cover letter (refer to section VII) and should include the following sections:

Section 1: Proposed Plan for COA Qualification

The following areas should be addressed for CDER review. The extent of information provided in each section will vary depending upon the evidence currently available to address each issue. We recommend for your initial briefing package you focus on the materials in section 1.1 to 1.6 below in order to facilitate discussion with the agency to ensure agreement before engaging in additional research. The additional information described below can be submitted in future submissions.

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 us e 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)

Identify targeted labeling or promotional claims based on the COA (i.e., proposed claim wording)

Provide a hypothesized conceptual framework for the outcome assessment(s)

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.

1.4 Critical details of the measure to the degree known

Reporter, if applicable

Item content or description of the measure

Mode of administration

Data collection method

1.5 Overview of current COA development status (for existing measures or for measures already under development)

1.6 Description of the involvement of external expertise, including scientific communities or other international regulatory agencies, if applicable

Section 2: Summaries of Planned Studies or Completed Studies

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

Development of the measure

- Literature input
- Expert input
- 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)
- Other input
- Justification for scoring algorithm (e.g., for multi-item COAs, the rationale and algorithm for how the items and domains are combined into a single score)
- For COAs with multiple versions, process for establishing that content validity is comparable between versions (e.g., COAs with multiple administration modes or methods)

2.2 Cross-sectional evaluation of measurement properties

Score reliability (including test-retest or inter-rater reliability, internal consistency)

Construct validity (comparison with other measures, e.g., patient and clinician global assessments)

2.3 Longitudinal evaluation of measurement properties

Longitudinal construct validity

Ability to detect change

2.4 Longitudinal evaluation to provide guidelines for interpretation of trial results

Evaluation of clinically meaningful within-patient change (e.g., responder definition(s))

2.5 Language translation and cultural adaptation, if applicable

Process for simultaneous development of versions in multiple languages or cultures

Process for translation/adaptation of original version

Evidence that content validity is similar for versions in multiple languages

2.6 User manual, as available

Summary of current experience and known measurement properties in the targeted context of use

Administration procedures

Training materials

Scoring, including how missing data will be handled as well as interpretation procedures

Copy of all versions of the COA (or screen shots, if applicable)

2.7 Appendices (may include)

List of references and copies of only the most important references that the submitter feels CDER reviewers may want to review

Study documents (e.g., protocols, analysis plan, interview guide, data collection form(s), screenshots if using an ePRO)

Note: The link to appendices should be embedded in the relevant summaries.

Section 3: Questions

Specific questions for CDER