Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000140: PROMIS Itch Questionnaire – Children Symptom (PIQ-C-Symptom)
Letter of Intent

Section 1. Administrative Structure

This project has been led by Amy Paller, MD (PI of sub-study that developed the PIQ-C and co-PI of the PEPR project at Northwestern University) from the Dermatology and Pediatrics departments at Northwestern University (676 N. St. Clair, Suite 1600, Chicago, IL 60611) and Jin-Shei Lai, Ph.D. (contact co-PI of the PEPR project at Northwestern University) from the Medical Social Sciences and Pediatrics departments at Northwestern University (625 N. Michigan Avenue, 21st floor, Chicago, IL 60611).

Dr. Paller has had 35 years of experience in caring for children with disorders causing itch. She is Chair of the Dept. of Dermatology, directs the Skin Disease Research Center at Northwestern (now Skin Biology and Diseases Resource-based Center) as well as the Pediatric Dermatology Clinical Research Unit, and has been the PI of more than 100 clinical trials in children with disorders associated with pruritus (atopic dermatitis, epidermolysis bullosa, ichthyosis, psoriasis), most of which involve measuring itch and quality of life. She has authored more than 250 peer-reviewed papers related to these disorders. She has been working on developing and validating PRO tools during the past 5 years, including through this project. Dr. Lai has significant experience in patient reported outcomes, including burden of disease and treatment impact studies across a range of pediatric and adult conditions. She has served as a principal investigator and co-investigator on several federal and foundation funded projects and is the lead developer of several pediatric and adult quality of life and symptom measurement instruments, including the PROMIS Fatigue and Cognition item banks for both adults and children, pediatric Neuro-QoL measurement system, and the pediatric Functional Assessment of Chronic Illness Therapy (pedsFACIT). Dr. Lai's PRO experiences have extended to adults and children with itch conditions. Particularly related to this submission, Dr. Lai co-authored the development of the PROMIS Itch Questionnaire - Adult (PIQ),[1-3] the Childhood Atopic Dermatitis Impact Scale (CADIS),[4] Skindex-Teen,[5] and Infantile Hemangioma Quality-of-Life (IH-QoL).[6-8] In the current proposal, Drs. Paller and Lai will use their accumulated experience in clinical care and research related to itch, PRO development, and expertise in measurement to direct the overall scientific and administrative integrity of the project. Other working group members include Dr. David Cella and Dr. Cindy Nowinski; both of whom are members of the Northwestern PEPR team with extensive experience in instrument development and FDA qualification processes

Section 2. Concepts of interest for meaningful treatment benefit

Pruritus, or itch, is the most common skin disease symptom and is listed among the 50 "common causes of disease", with a global prevalence of almost 280 million persons.[9] Itch can result from various diseases and/or treatment;[10] among them, itch is one of primary concerns on children with atopic dermatitis. Atopic dermatitis (known to the lay public as "eczema") has a prevalence of almost 230 million persons and is also among the top 50 disorders in terms of prevalence. Itch is the predominant symptom and may profoundly impact sleep and quality of life[11] in affected children,[12,13] with the degree of impact varying as a function of the intensity of itch symptoms.

Itch is also a disabling feature of a wide variety of other chronic disorders affecting children,[14] among them primary skin disorders with inflammation (e.g., chronic urticaria[15] and psoriasis, and genetic disorders such as epidermolysis bullosa[16,17] and ichthyosis, in addition to atopic dermatitis), infiltrative disorders (e.g., mastocytosis), infestations[18] (such as scabies), drug reactions (with or without clinical inflammation), burns,[19] and systemic disorders (e.g., liver disease,[20] neurologic dysfunction, Hodgkin/non-Hodgkin lymphoma,[21] neurofibromas,[22] and renal disease[23]). Having itch in these disorders can also lead to sleep disturbance, pain and secondary skin infection related to disruption of the skin barrier from frequent scratching. In many cases, the underlying disorder associated with itch is congenital or begins during infancy, translating into long-term compromise in quality of life. However, few itch/pruritus scales, especially that comprehensively cover itch symptoms, have been validated for use in children.

Given the literature mentioned above, our clinical experiences, results from interviewing children with itch and their parents[24], and the PROMIS domain framework, we have proposed a conceptual model as shown in the Figure 1. Biological and physiological factors (e.g., skin inflammation of various types) and/or environmental triggers (e.g., heat and sometimes climate change) can trigger and/or exacerbate itch in children with pruritic disorders.

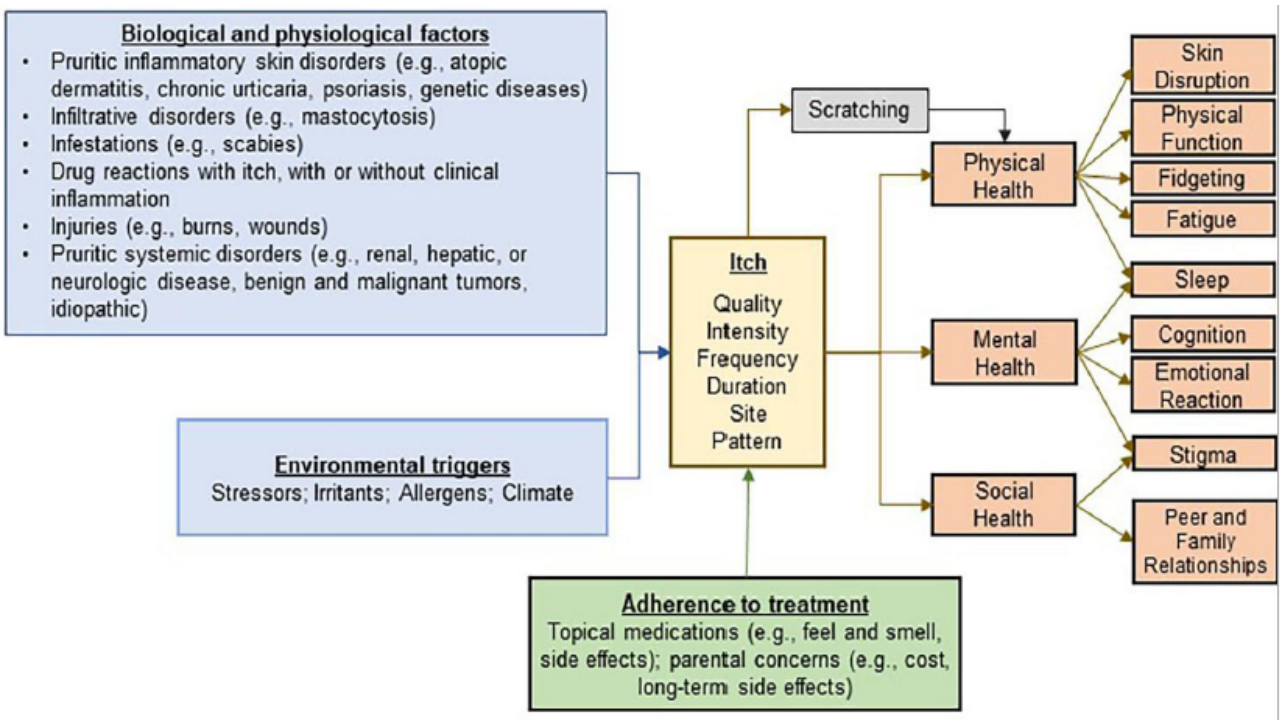

Figure 1. Conceptual Model

Section 3. Context of use for COA qualification

a. **Targeted study population including a definition of the disease and anticipated selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)**

The proposed measures, **PIQ-C-Symptom PRO** and **the PIQ-C-Symptom** ObsRO, target children with cutaneous disorders (PRO: reported by children with ages 8 and older; ObsRO: reported by parents of children with ages 5 years and older). The **PIQ-C-Symptom** is intended for use as a secondary endpoint in clinical trials assessing therapeutics for itch (i.e., symptoms). Itch (also called pruritus) is defined as an unpleasant sensation that elicits scratching. Itch is a symptom commonly experienced by patients with cutaneous disorders such as atopic dermatitis, ichthyosis, epidermolysis bullosa, and other skin disorders.

b. **Targeted study design and statistical analysis plan (includes the role of the planned clinical outcome assessment in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate)**

Data collection for the validation of the **PIQ-C-Symptom** (both PRO and ObsRO) in a trial of more than 200 children, has been completed. Significant correlations with known measures, ability to distinguish between severity groups, and responsiveness across time suggest clinical validity. Data analysis specific to the

PIQ-C-Symptom is in progress. The Spanish translation of the **PIQ-C Symptom was** completed for both the PRO and ObsRO versions. We will be poised to validate in children with cutaneous disorders with the plan to test a Spanish version in the US next. The **PIQ-C-Symptom** can then be implemented in trials for a wide variety of pruritic skin disorders. At this time, numerous new medications to target atopic dermatitis and other pruritic inflammatory skin disorders (e.g., psoriasis, ichthyosis, epidermolysis bullosa) are being developed, with testing initially in adults and then in adolescents and children. To date, these trials are evaluating itch by using a single itch item. A single itch item cannot measure children's itch experiences in a comprehensive manner.

c. Applicable study settings for future clinical trials

i. Geographic location with language/culture groups

PIQ-C-Symptom will be available in English, Spanish, and possibly other languages in the future. The initial trials will be limited to the US and will be extended to international trials once other language versions are available.

ii. Other study setting specifics (e.g., inpatient versus outpatient)

The Context of Use is unrestricted to patient context, culture, and treatment setting.

Section 4. COA type [Patient-reported outcome (PRO), Clinician-reported outcome (ClinRO), Observer-reported outcome (ObsRO), performance outcome (PerfO) measure, or Other]

The proposed form is a Patient-reported outcome (PRO) and an Observer-reported outcome (ObsRO) via parent proxy report.