THE PEPR CONSORTIUM
ADVANCING THE SCIENCE OF PEDIATRIC PATIENT-REPORTED OUTCOMES FOR CHILDREN WITH CHRONIC DISEASES

HealthMeasures User Conference
September 27-28, 2017
Northwestern University
Prentice Women’s Hospital
Chicago, Illinois

The PEPR Consortium is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) through grant numbers U19AR09525, U19AR09522, U19AR09519 & U19AR09526.
Agenda

*Introduction to PEPR: Mission, Structure, Website, IOF Projects*: 10:00-10:15 am
  Brandon Becker, PhD, MPH

*Research Projects at Northwestern University*: 10:15-10:23 am
  Richard Gershon, PhD

*Research Projects at Duke University*: 10:23-10:31 am
  Laura Schanberg, MD

*Research Projects at Children’s Hospital of Philadelphia*: 10:31-10:39 am
  Brandon Becker, PhD, MPH

*Research Projects at Medical College Wisconsin*: 10:39-10:47 am
  Brandon Becker, PhD, MPH

*FDA Qualification*: 10:47-10:55 am
  Carole Tucker, PT, PhD
  Michelle Campbell, PhD

*Concluding Remarks and Future Directions*: 10:55-11:05 am
  Jim Witter, MD, PhD
Mission

• To validate existing and emerging pediatric item banks available through the NIH Patient-Reported Outcomes Measurement Information System (PROMIS®) in clinical research and care settings

• Long-term goals
  • Develop reliable, validated clinical tools for pediatric patient reported outcomes (PROs) to improve the assessment of outcomes in clinical trials or other research settings in order to personalize the ongoing care of children with chronic conditions
  • Examine the impact of environmental stressors on children’s health including their symptoms and quality of life
4 Centers of Excellence  6 Performance Sites  82 Collaborating Sites  11 Chronic Conditions

23 PROMIS® Instruments
PROMIS® Measures

- PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children.

- Can be used with the general population and with individuals living with chronic conditions.
PROMIS® Measures

- Asthma Impact
- Global Health
- Anxiety
- Depressive Symptoms
- Positive Affect
- Life Satisfaction
- Meaning & Purpose
- Psychological Stress Experiences
- Physical Stress Experiences
- Pain Interference
- Pain Behavior
- Pain Quality
- Pain Intensity
- Fatigue
- Family Relationships
- Peer Relationships
- Physical Functioning
- Physical Activity
- Strength Impact
- Itch*
- Sleep Disturbance**
- Stigma**
- IBD GI Symptoms**

*under development
**new measure
The Pediatric Patient Reported Outcomes in Chronic Diseases (PEPR) Consortium, funded by the National Institutes of Health (NIH) and administered by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), is dedicated to the clinical validation of pediatric patient-reported outcomes (PROs) among children with chronic diseases.

NIAMS issued a Request for Applications (RFA) in March 2015 which resulted in a consortium consisting of four Centers of Excellence: The Children's Hospital of Philadelphia, Northwestern University, Medical College of Wisconsin and Duke University. The purpose of our research is to capitalize on recent advances in the science of PROs to improve pediatric health and well-being by capturing the voice and experience of children and their families living with a variety of chronic conditions.
Infrastructure and Opportunities Fund (IOF)

**Purpose:** To administer and support resources that provide additional financial assistance or technical expertise for projects undertaken by PEPR investigators.

- **Using Geographic Information System (GIS) to Assess Social and Environmental Effects on Children with Chronic Disease**
- **Evaluating the Association between Activity and PROMIS measures in Children with Chronic Conditions**
NORTHWESTERN UNIVERSITY
Asthma and Atopic Dermatitis Validation of PROMIS Pediatric Instruments (AAD-PEPR)

HealthMeasures Conference
September 27, 2017

This project is supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) grant # 1U19AR069526-01
Asthma prevalence among children 0 to 17 years of age in the United States, in 1980-2007

Specific aims:

I. Validate PROMIS measures

1. well characterized samples of children with asthma

2. who span a wide range of ages,

3. settings (general population, office and hospital)

4. and disease severity.

5. Measures will be validated against clinical measures of disease severity, disease control, and other validated patient-reported outcome assessments.
Specific aims:

II. Examine responsiveness of PROMIS to detecting clinically significant change in disease status, and estimate the minimally important differences
Specific aims:

III. Evaluate whether perceived stress as measured by PROMIS is associated with altered asthma control and related health outcomes. Evaluate potential Differential Item Functioning (DIF) based on clinical and demographic measures.
The Trials:

Figure 1. AAD-PEPR Accrual

- SICAS-2
  - N=300
  - Inner City Schools
  - AA, Hispanic
  - English/Spanish

- CHICAGO
  - N=640
  - Hospital ED
  - AA, Hispanic
  - English/Spanish

- ASIST
  - N=200
  - Community Providers
  - AA
  - English

N=250

N=225

N=170

AAD-PEPR

- N=645
- Diverse settings & asthma severity
- Race/ethnicities most affected by Asthma
- English/Spanish
The Trials: SICAS 2

School Inner-City Asthma intervention Study
SICAS-2- NIAID U01 AI 110397

Wanda Phipatanakul, MD, MS, PI
Boston Children’s Hospital
Harvard Medical School
Boston Public Schools
SICAS 2 Goal

Determine the effectiveness of a
CLASSROOM (Air Purifiers)
SCHOOL (IPM/Cleaning)
Environmental Intervention to
REDUCE asthma morbidity in inner-city
school children with asthma
The Trials: CHICAGO PLAN
The Trials: CHICAGO PLAN

1) Complete planning activities, including qualitative interviews with caregivers, clinicians, and community health workers (CHWs), to finalize the study design and protocol, and obtain clearances from all institutional and community partners for the CHICAGO Trial.

2) Conduct a 3-arm multi-center pragmatic trial comparing the effectiveness of:
   1) Provider-ED
   2) Provider-ED combined with a patient-level CHW-led intervention
   3) Usual Care

Secondary analyses - heterogeneity of treatment effects
Secondary aim:
3) Identify barriers and facilitators to inform subsequent implementation studies.
### Measures:

<table>
<thead>
<tr>
<th>Type</th>
<th>Measure</th>
<th>Baseline</th>
<th>1 Month</th>
<th>6 Month</th>
<th>12 Month</th>
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<td>PROMIS Pediatric Profile- 25- Child</td>
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<td>Maximum Asthma Symptom Days/2 weeks</td>
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<td>PROMIS Adult Short Forms: Anxiety, Depression, Sleep</td>
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<td>Disturbance, Fatigue</td>
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<td>PROMIS Satisfaction with Social Roles</td>
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**KEY:** CHICAGO Plan = C; ASIST = A; SICAS-2 = S
Planned Analyses:

### Table 4: Convergent Validity Correlations for PROMIS Measures

<table>
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<th>Convergent Validity</th>
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<td>X</td>
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<td>FEV1</td>
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<tr>
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<td>EQ-5D</td>
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<td>Cortisol (baseline only)</td>
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<td>PSS</td>
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<td>Healthcare Utilization</td>
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<td>PACQLQ</td>
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</table>

Abbreviations: ACT/cACT = [Childhood] Asthma Control Test; Anx SF-4 = PROMIS Anxiety 4-item Short Form; CHSA = Children's Health Survey for Asthma; Dep SF-4 = PROMIS Depression 4-item Short Form; FEV1 = Forced Expiratory Volume; GH-7 = PROMIS Global Health; Mob SF-4 = PROMIS Mobility 4-item Short Form; PACQLQ = Pediatric Asthma Caregiver's Quality of Life Questionnaire; PAIS = PROMIS Asthma Impact Scale; PSE SF-4 = PROMIS Psychological Stress Experiences 4-item Short Form; PSS = Perceived Stress Scale.
Planned Analyses:

<table>
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<tr>
<th>Convergent Anchor</th>
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<td>EQ-5D</td>
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Table 5: MID Anchors for PROMIS Measures

<table>
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<tr>
<th>Convergent Anchor</th>
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<tr>
<td>ACT/cACT</td>
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<td>Children’s Stress Assessment</td>
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<td>EQ-5D</td>
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Provider-based adjustment (PBA)

12 months

Run-in

Randomization

- Asthma coaching on albuterol use

Symptom based adjustment (SBA)

Study visits by unblinded and blinded staff

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**Pre-screen**
- By phone (0w)
- Verbal Consent
- Med history
- AEQ

**V1 (0-4w)**
- Consent
- AEQ
- FEV1
- Asthma education
- Height/weight
- Drug for run in
- Diary
- PE

**RZ: V2 (3-5W)**
- AEQ
- ACT
- CHS, PROMIS
- FEV1
- Randomization
- Open label drug
- Instruction of treatment arms
- PE if not done V1

**V3 (5-7w)**
- (By phone: blinded study staff)
- Safety review

**V4, V5, V6**
- (3, 6, 9mos: blinded staff)
- ACT
- PROMIS
- Review exac
- Collect drugs
- Drug dispense
- Collect 4 wk diary (*6mo only)

**V7**
- (12mos: blinded staff)
- ACT
- CHS, PROMIS
- FEV1
- Height/weight
- Review exac
- Collect drugs
- Satisfaction quest.
- Medication review
- Collect of 4 wk diary

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**PCP study visit**

4-6 weeks f/u
- (By PCP)
- Clinical review of their condition
- Treatment arm re-instruction

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**PCP visits per routine care**

- Clinical visits by PCP in both arms per routine practice
- Review of control, events, adherence to treatment arms
- Review/record current meds
- PCP visit/exit questionnaire
AAD-PEPR: Asthma and Atopic Dermatitis Validation of PROMIS Pediatric Instruments

Amy Paller, MS, MD, PI
Depts of Dermatology and Pediatrics
Northwestern University Feinberg School of Medicine
Rationale

- Atopic dermatitis is a common inflammatory skin disorder that affects ~17% of US children.
- 37% have moderate to severe disease, with disproportionately greater severity in minority children.
- Personal and environmental stressors are recognized exacerbants.
- Attention to developing new therapies for AD is growing, but there is an incomplete understanding of impact of the disease and effect of treatment on quality of life.
Goals

• **Evaluate the validity, reliability and responsiveness of the pediatric PROMIS measures for AD**

• **Specific Aims**
  1. Using mixed methods approach and PROMIS standards, develop and calibrate a pediatric itch item bank (5-17 y/o)
  2. Validate generic PROMIS measures, the new Itch measure (PIQ-C), and Stigma in our AD children
  3. Examine the sensitivity of PROMIS in detecting change in disease status and estimate minimally important differences for PROMIS measures in AD children
  4. Investigate the impact of environmental stressors by evaluating differences based on presence of bacterial infection, race/ethnicity, and family income
Enhancing Clinical Meaningfulness and Usefulness of PROMIS Pediatric Measures via Validation in Children and Adolescents with Rheumatic Disease, Cancer, or Inflammatory Bowel Disease
Overall Project Goals

Enhance the clinical meaningfulness and usefulness of legacy and newly developed PROMIS Pediatric measures and other PRO measures, in order to:

1. Facilitate the scientific evaluation of the experience of childhood chronic illness

2. Foster PRO use in clinical and research settings

3. Improve outcomes of care by integrating the patient voice
Administrative Core
Bryce Reeve, PhD & Laura Schanberg, MD

Research Project 1: Clinical Validation of PROMIS Pediatric Measures in Diverse Research Networks
Elissa Weitzman, ScD, MSc
Bryce Reeve, PhD

Research Project 2: Enhancing Meaningfulness and Usefulness of Pediatric and Caregiver PROMIS Measures across Illness Groups
Pam Hinds, PhD, RN
Emily Von Scheven, MD, MAS

Cancer
N=480

IBD
N=500

JIA/SLE
N=450

Data Management Core
Antonia Bennett, PhD
Research Project 1: Clinical Validation of PROMIS® Pediatric Measures in Diverse Research Networks

- **Aim 1: RESPONSIVENESS**
  - Evaluate the responsiveness of the PROMIS Pediatric measures to measure change in HRQOL over time and its association with clinical anchors and patient-reported symptom toxicities.

- **Aim 2: PREDICTION**
  - Evaluate whether PROMIS measures of depression and anxiety are associated with subsequent measures of health status including physical and social functioning, disease-specific outcomes and substance use, after adjusting for relevant measures of baseline health status.

- **Aim 3: DIRECT OBSERVATION**
  - Determine the association between steps taken (pedometer data) and PROMIS Pediatric measures in order to explore the use of pedometry data to augment PROs in research and clinical care.
PROMIS Pediatric Domains Framework

**Profile Domains**
- Physical Health
  - Mobility
  - Upper Extremity Function
  - Pain Interference
  - Pain Intensity
  - Fatigue

**Profile Domains**
- Mental Health
  - Depressive Symptoms
  - Anxiety

**Profile Domains**
- Social Health
  - Peer Relationships

**Additional Domains**
- Asthma Impact
- Pain Behavior
- Pain Quality
- Physical Activity
- Physical Stress Experiences
- Strength Impact

**Additional Domains**
- Anger
- Life Satisfaction
  - Meaning and Purpose
  - Positive Affect
  - Psychological Stress Experiences
Clinical Anchor Measures

- Disease activity measures (MD- and self-report)
  - Global Impression of Change
  - Validated disease measures (Cancer, IBD, JIA, SLE)
- Substance Use
  - Ages 13-18
  - Quantity and Frequency of Alcohol and Marijuana Use
- Wearable device
  - Pedometer

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<th>More Prevalent AEs captured by PRO-CTCAE Item Library</th>
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<tr>
<td>Headache</td>
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<td>Hoarseness</td>
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<td>Alopecia</td>
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<td>Dysphagia</td>
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<td>Hyperhidrosis</td>
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<td>Blurred vision</td>
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<td>Edema limbs</td>
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<td>Memory Impairment</td>
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Other AEs captured by PRO-CTCAE Item Library

| Abdominal distension                                |
| Dyspepsia                                            |
| Hoarseness                                           |
| Alopecia                                             |
| Dysphagia                                            |
| Hot flashes                                          |
| Arthralgia                                           |
| Dyspnea                                              |
| Hyperhidrosis                                        |
| Blurred vision                                       |
| Edema limbs                                          |
| Memory Impairment                                    |
| Bruising                                             |
| Epistaxis                                            |
| Myalgia                                              |
| Chills                                               |
| Fall                                                 |
| Palpitations                                         |
| Concentration impairment                             |
| Fecal incontinence                                   |
| Photosensitivity                                     |
| Dizziness                                            |
| Fever                                                |
| Pruritus                                             |
| Dry eye                                              |
| Flashing lights                                      |
| Rash acniform                                        |
| Dry mouth                                            |
| Flatulence                                           |
| Restlessness                                         |
| Dry skin                                             |
| General muscle weakness                              |
| Voice alteration                                     |
| Dyspeusia                                            |
| Hiccups                                              |
| Skin ulceration                                      |
| Dry skin                                             |
| General muscle weakness                              |
| Watering eyes                                        |

| Abdominal distension                                |
| Dyspepsia                                            |
| Hoarseness                                           |
| Alopecia                                             |
| Dysphagia                                            |
| Hot flashes                                          |
| Arthralgia                                           |
| Dyspnea                                              |
| Hyperhidrosis                                        |
| Blurred vision                                       |
| Edema limbs                                          |
| Memory Impairment                                    |
| Bruising                                             |
| Epistaxis                                            |
| Myalgia                                              |
| Chills                                               |
| Fall                                                 |
| Palpitations                                         |
| Concentration impairment                             |
| Fecal incontinence                                   |
| Photosensitivity                                     |
| Dizziness                                            |
| Fever                                                |
| Pruritus                                             |
| Dry eye                                              |
| Flashing lights                                      |
| Rash acniform                                        |
| Dry mouth                                            |
| Flatulence                                           |
| Restlessness                                         |
| Dry skin                                             |
| General muscle weakness                              |
| Voice alteration                                     |
| Dyspeusia                                            |
| Hiccups                                              |
| Skin ulceration                                      |
| Dry skin                                             |
| General muscle weakness                              |
| Watering eyes                                        |
| Dyspeusia                                            |
| Hiccups                                              |
| Skin ulceration                                      |
| Dry skin                                             |
| General muscle weakness                              |
| Watering eyes                                        |
1) How often did you have **pain**?
   - never
   - sometimes
   - most of the time
   - almost all the time

2) How bad was your **pain**?
   - did not have any
   - a little bad
   - bad
   - very bad

3) How much did **pain** keep you from doing things you usually do?
   - not at all
   - some
   - a lot
   - a whole lot
Longitudinal Study

Child / Adolescent

Parent (proxy)

Clinician (proxy)

Baseline ($T_1$) → Follow-up ($T_2$) → Follow-up ($T_3$)

High symptoms → Low symptoms → High symptoms

Low symptoms → High symptoms → Low symptoms
Research Project 2: Enhancing Meaningfulness and Usefulness of Pediatric and Caregiver PROMIS® Measures across Illness Groups

• **Aim 4: SUBGROUP ANALYSIS**
  • Identify unobserved subgroups of children with rheumatic disease, cancer, or IBD with respect to physical and mental health (as measured by PROMIS) using latent profile analysis and latent transition analysis.

• **Aim 5: MINIMALLY IMPORTANT DIFFERENCES**
  • Estimate a clinically minimally important difference (MID) in change in PROMIS Pediatric scores from the child’s perspective.

• **Aim 6: CLINICAL CUT SCORES**
  • Identify clinical cut scores (or thresholds) along the PROMIS Pediatric T-score metric associated with varying levels of symptom severity and functional status using standard setting methods with key stakeholders (adolescents, parents, and clinicians).
Minimally Important Difference (MID)

- MID as the point at which 50% of participants (clinicians, patients, parents) would declare an important change
- Previous study in PROMIS pediatric measures:
  - clinicians MID = 2 pts, patients & parents MID = 3 pts

(Thissen et al., 2015)

Please decide if you think these responses show that this child is...
- At least a little better today
- Essentially no different
- At least a little worse today.
5 Fatigue Vignettes with Bookmark Placement

Jim’s Energy

Jill’s Energy

Tom’s Energy

Sam’s Energy

Kelly’s Energy

In the last 7 days, Kelly was never so weak that she had to limit her social activities, was unable to leave the house, or needed help doing her usual activities.

In summary, Kelly reports during the past 7 days:

How often did you have to limit your social activities because of your fatigue?

Never  Rarely  Sometimes  Often  Always

How often were you too tired to leave the house?

Never  Rarely  Sometimes  Often  Always

I need help doing my usual activities.

Not at all  A little bit  Somewhat  Quite a bit  Very much

Severe Fatigue

Moderate Fatigue

Mild Fatigue

No Fatigue
Where are clinically meaningful thresholds on the PROMIS scale?
Significance and Innovation

- Validating a broad range of PROMIS measures in 3 chronic illnesses to better understand the experience of pediatric patients and caregivers using legacy measures and clinical data
  - Traditional PRO domains
  - Adverse event reporting
- Focus on meaningfulness of the measures to promote use in clinical practice and research
- Next steps include using data to develop a “dashboard” to help health care providers interpret the measures in easy format.
- Validate in younger children and Spanish speakers.
WHO
We Are

PEPR Investigators
Bryce Reeve, PhD – PI (Duke)
Laura Schanberg, MD – PI (Duke)
Mike Kappelman, MD – Co-I (UNC, IBD)
Millie Long, MD – Co-I (UNC, IBD)
Antonia Bennett, PhD – Co-I (UNC)
Emily von Scheven, MD (UCSF, Rheumatic)
Sarah Ringold, MD (Seattle Children’s, Rheumatic)
Elissa Weitzman, ScD, MSc (Boston, Rheumatic)
Pamela Hinds, RN, PhD, FAAN (Children’s National, Cancer)
Janice Withycombe, PhD, RN, MN, CCRP (Emory, Cancer)
Jichuan Wang, PhD (Children’s National)
Crohn’s Disease Project:

- 65 randomized patients ➔ Target 425 (319)
- 40 participating sites

**Instruments:**
- Pain Interference
- Fatigue
- Positive Affect
- IBD GI symptoms
Chronic Kidney Disease Project:

- Target 200 Parent-child dyads
- 18 Participating Sites

Instruments:
- Fatigue
- Sleep Disturbance
- Sleep-Related Impairment
- Life Satisfaction
- Meaning and Purpose
- Psychological Stress Experiences
Meet the **MyKidneyHealth** study team:

Chris Forrest, MD, PhD  
Principal Investigator

PRO measures are the best way to hear the voices of children about their own health.

Brandon Becker, PhD  
Study Director

PROs give us the opportunity to measure wellbeing from the patient’s perspective, which is important for understanding their quality of life.

Anna de la Motte, MS  
Study Coordinator

Hi, I’m Anna and I’m interested in how we can meaningfully engage you as participants. I’ll be communicating with you throughout the project via email, phone call and text. Don’t hesitate to reach out with any questions or concerns you may have!

Jenn Clegg, MA  
Study Coordinator

This study is an important step in getting pediatric PROs into the hands of more clinicians. PROs help elevate doctors’ understanding of how chronic illness affects their patient’s lives and gives them the tools to help better care for the whole person and not just treat the illness. In pediatrics, this is huge.

Macy Marcucci  
Study Coordinator

Your experiences matter! This study will help us learn about how your condition influences your experiences of sleep, fatigue, life satisfaction and stress. Ultimately, it will help doctors understand and treat their patients based on their reports of wellbeing in addition to their physical symptoms.
What to expect in the MyKidneyHealth study:

- Parents and youth (ages 8-17) will complete a total of 7 questionnaires over the span of 2 years:
  - Baseline survey
  - 3-month survey
  - 6-month survey
  - Year 1 survey
  - 15-month survey
  - 18-month survey
  - Year 2 survey

- You will receive the following messages:
  - Questionnaire reminders
  - Gift card information
  - Health tips and information
The MyKidneyHealth participating site locations across the US and Canada:
Cancer Survivors project:

- Recruiting 300 Parent-child dyads
- 25 dyads enrolled since Aug 2017
- 1 site

- Instruments:
  - Pain interference
  - Fatigue
  - Psychological Stress
  - Positive Affect
  - Meaning and Purpose
  - Stigma
  - Anxiety
  - Depression
MEDICAL COLLEGE
WISCONSIN
Midwest Child Patient Reported Outcomes Consortium (M-cPROs)

Administrative Core
Julie Panepinto

Internal Advisory Committee
Project Leaders
Core Leaders

External Advisory Committee
Roy Silverstein MD
Michael DeBaun MD, MPH
Alex Wong PhD

Research Project 1
Julie Panepinto, PI

Research Project 2
Elizabeth Cox, PI
Kathryn Flynn, Co-PI
Overall Goals

• Advance the understanding and measurement of child patient reported outcomes (cPROs) in children with chronic disease using PROMIS

• Allow for widespread use of cPROs in both clinical care and research in order to optimize the well-being and functioning of these children
Study Focus

• Validation and meaningful differences

• Impact on c-PROs over time
  • Disease-related factors
  • Family relationship
  • Environmental stressors
Acute Disease Exacerbation

- Sickle cell disease-painful crisis
- Asthma-asthma exacerbation
- Diabetes-diabetic ketoacidosis
- Assessing c-PROs
  - In ED at presentation
  - One week post discharge
  - 1-3 months post discharge
Longitudinal Cohort

Every 6 month assessments for 3 years

- PROMIS Profile 25
- New PROMIS measures
  - Physical Stress Experiences
  - Pain Behavior
  - Pain Quality Sensory
  - Pain Quality Affective
  - Family Relationships
  - Physical Activity
  - Strength Impact
- Asthma Impact
## Recruitment

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<th></th>
<th>ASTHMA</th>
<th>DIABETES</th>
<th>SICKLE CELL DISEASE</th>
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<td>Longitudinal cohort (Clinic)</td>
<td>104</td>
<td>140</td>
<td>115</td>
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<tr>
<td>Acute disease exacerbation (ED)</td>
<td>120</td>
<td>55</td>
<td>66</td>
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<tr>
<td>TOTAL*</td>
<td>222</td>
<td>193</td>
<td>152</td>
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</tbody>
</table>

**TOTAL RECRUITED = 567**

*Some subjects are in multiple cohorts*
FDA QUALIFICATION
PEPR FDA Workgroup Objectives

• Primary Aim:
  • To qualify select PEPR instruments as PRO Clinical Outcomes Assessment (COA) through the FDA Drug Development Tool Qualification Program

• Secondary:
  • To advance maturation of PROMIS pediatric instruments
  • To develop familiarity with FDA COA qualification process as a gateway for other PROMIS pediatric measures
FDA: Drug Development Tools Qualification Program

- The Drug Development Tool (DDT) Qualification Programs allow CDER to work with submitters to guide them as they develop or refine a DDT for a specific context of use. CDER then will rigorously evaluate the submission for use in the regulatory process.

- Qualifying a DDT will allow sponsors to use the DDT in the qualified context of use during drug development without requesting that CDER reconsider and reconfirm the suitability of the DDT for the qualified context of use.

- 11:30 – 12:30 Plenary Today
  - Michelle Campbell PhD, Center for Drug Evaluation & Research (CDER), US FDA
COA qualification: COA qualification is based on a review of the evidence to support the conclusion that the

COA is a well-defined and reliable assessment of a specified concept of interest for use in adequate and well-controlled (A&WC) studies in a specified context of use.

COA qualification represents a conclusion that within the stated context of use, results of assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making and labeling.

For COAs that do not provide evidence of how patients feel, or function in daily life, qualification also includes a review of the evidence that the concept assessed is an adequate replacement for how patients feel or function in daily life.
Qualification of CLINICAL OUTCOME ASSESSMENTS (COAs)

- Identify Context of Use (COU) and Concept of Interest (COI)
- Draft Instrument and Evaluate Content Validity
- Cross-sectional Evaluation of Other Measurement Properties
- Longitudinal Evaluation of Measurement Properties/Interpretation Methods
- Modify Instrument
Roadmap to
PATIENT-FOCUSED OUTCOME MEASUREMENT
in Clinical Trials

1. Understanding the Disease or Condition
   A. Natural history of the disease or condition
   B. Patient subpopulations
   C. Health care environment
   D. Patient/caregiver perspectives

2. Conceptualizing Treatment Benefit
   A. Identify concept(s) of interest (COI) for meaningful treatment benefit
   B. Define context of use (COU)
   C. Select clinical outcome assessment (COA) type

3. Selecting/Developing the Outcome Measure
   A. Search for existing COA measuring COI in COU
   B. Begin COA development
   C. Complete COA development
PEPR ~ FDA/COA Points

- Context of Use
  - FDA → Condition Focused
  - PROMIS → Broader application
- Focus on PROs that are more common as primary/proximal (drug) clinical trial endpoints
- Current efforts on specific instruments (fixed length forms) versus item banks or CAT versions
- Staged, iterative process between PEPR & FDA CDER
Pediatric PROMIS Domains

PROMIS® Pediatric Self- and Proxy-Reported Health

- Physical Health
  - Fatigue
  - Mobility
  - Pain Intensity
  - Pain Interference
  - Upper Extremity Function

- Mental Health
  - Anxiety
  - Depressive Symptoms

- Social Health
  - Peer Relationships

PROMIS Profile Domains

- Asthma Impact
- Pain Behavior
- Pain Quality
- Physical Activity
- Physical Stress Experiences
- Strength Impact

PROMIS Additional Domains
PEPR COA Qualifications- Overview

• Conditions
  • Chronic Kidney Disease
  • Crohn’s Disease

• Measures **
  • PROMIS Pediatric Pain Interference Short Form 8 (SF8)
  • PROMIS Pediatric Fatigue Short Form 8 (SF8)
  • PROMIS Pediatric Sleep Disturbance Short Form 8 (SF8)
  ** SF items differ slightly from the parallel standard short form based on qualitative work in the 2 conditions
<table>
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<tr>
<th>Instrument</th>
<th>Condition</th>
<th>COA DDT #</th>
<th>Stage &amp; Next Step</th>
<th>Comments</th>
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<td>PROMIS Pediatric Short Form V1.0 – Crohn’s Specific Fatigue 8</td>
<td>Crohn’s Disease</td>
<td>COA DDT 000092</td>
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<td>Chronic Kidney Disease</td>
<td>COA DDT 000095</td>
<td>LOI Clarifications – 10/08/2017</td>
<td>Please provide a summary of the development of the PROMIS® Pediatric Short Form v1.0, including how the instrument’s 8 items were selected from the overall item bank. Please also submit any documentation of literature review, expert input, and reports of qualitative research with pediatric patients with CKD.</td>
</tr>
<tr>
<td>PROMIS Pediatric Short Form v1.0 – Crohn’s Specific Pain Interference 8</td>
<td>Crohn’s Disease</td>
<td>COA DDT 000093</td>
<td>LOI Clarifications - 10/08/2017</td>
<td>Please provide the development work of the PROMIS® Pediatric Pain Interference item bank. This can be provided either by a summary of the development or select literature. Additionally, explain how the 8 items of the pain interference short form submitted for review were selected from the overall item bank. Any documentation of qualitative reports of work with pediatric Crohn’s patients and their interpretation of pain interference should be submitted as well</td>
</tr>
<tr>
<td>PROMIS Pediatric Short Form v1.0 – CKD Specific Sleep Disturbance 8</td>
<td>Chronic Kidney Disease</td>
<td>COA DDT ######</td>
<td>LOI Submit 10/08/2017</td>
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<td>PROMIS Pediatric Short Form v1.0 - Pain Interference 8a</td>
<td>Chronic Kidney Disease</td>
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<td>---PEPR HOLD ----</td>
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<tr>
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<td>Crohn’s Disease</td>
<td>COA DDT 000097</td>
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Closing Remarks

-PEPR: Creating a Vision-
• 2017 HealthMeasures User Conference
• Global Pediatric Clinical Trials Network (RFA-FD-17-014)
• PROMIS pediatric measures submitted for qualification
Advancing Pediatric PRO clinical science

• Short/Intermediate Range Goals
  • Maximize synergies by addressing gaps and opportunities
  • Decide on judicious use of IOF funds to advance goals of PEPR
  • Establish an infrastructure to maximize collection and analyses of cPRO/proxy data
  • Create a collegial, exciting Consortium
Advancing Pediatric PRO clinical science

• Long-term Goals
  • Clinically validate cPROs/proxies to be able function as tools to reliably, easily and meaningfully assess symptoms and health-related quality of life
  • Better understand the impact of environmental stressors on pediatric well being and chronic diseases
  • Create and leverage opportunities with ECHO
  • Advance the FDA qualification of cPROs
    • For use as exploratory (or other) endpoints in industry trials
  • Gain new insights into how cPROs complement objective clinical data to assess health and disease
  • Be informative and transformative in pediatrics
PePConsortium.org

Imaging

Biomarkers/Labs

Observer-Reported Outcomes

Patient-Reported Outcomes

Clinician-Reported Outcomes

Performance Outcomes
Q &A