CLINICAL EVALUATION OF PROMIS PEDIATRIC PERSON-REPORTED OUTCOME MEASURES IN CHILDREN WITH CHRONIC KIDNEY DISEASE

1. OBJECTIVE

The primary objective is to examine the longitudinal associations between pediatric patient-reported outcome measures of health and clinical indicators of chronic kidney disease activity.

2. HYPOTHESIS

Pediatric patient-reported health will decline as children's kidney function declines.

CKD is characterized by progressive decline in kidney function,[3] which is expected to correlate with declines in subjective well-being. Prior studies suggest that poorer kidney function and subjective well-being are associated with recent hospitalization[1] and low eGFR (< 15).[2] This study will extend this work by assessing the associations between longitudinal trajectories of kidney function decline and self-reported well-being.

3. CONCEPTUAL FRAMEWORK

According to a 2013 National Research Council report, subjective well-being can be considered a multi-faceted concept with experiential (negative and positive emotional states), evaluative (how satisfying life is), and eudaimonic (sense of meaning and purpose) components.[4] Relieving suffering by reducing disease activity or palliating symptoms themselves to promote happiness, healthy development, and flourishing is often the objective of pediatric chronic care management. This is true for management of CKD, which is characterized by progressive loss of kidney function with concomitant increases in pain (headache, abdominal pain, chest pain), fatigue, and poor concentration.[5,6] Physical and emotional distress are significant problems for children with advanced CKD and on dialysis.[7-9] There is good evidence that positive and negative affect are not opposite ends of a single dimension,[10] so a treatment or disease state may have a marginal effect on a child's happiness but a substantial effect on suffering, and vice versa. Furthermore, the impact of kidney failure on children's well-being appears to increase as kidney function declines.[11-13] Roumelioti and colleagues found that children with a glomerular filtration rate lower than 30 had higher odds of reporting symptoms related to sleep and fatigue, which were associated with overall health-related quality of life.[5] Consistent with Wilson and Cleary's conceptual model of patient outcomes,[14] the evidence suggests that kidney disease symptoms affect functional status, which in turn affects quality of life (see Figure 1).

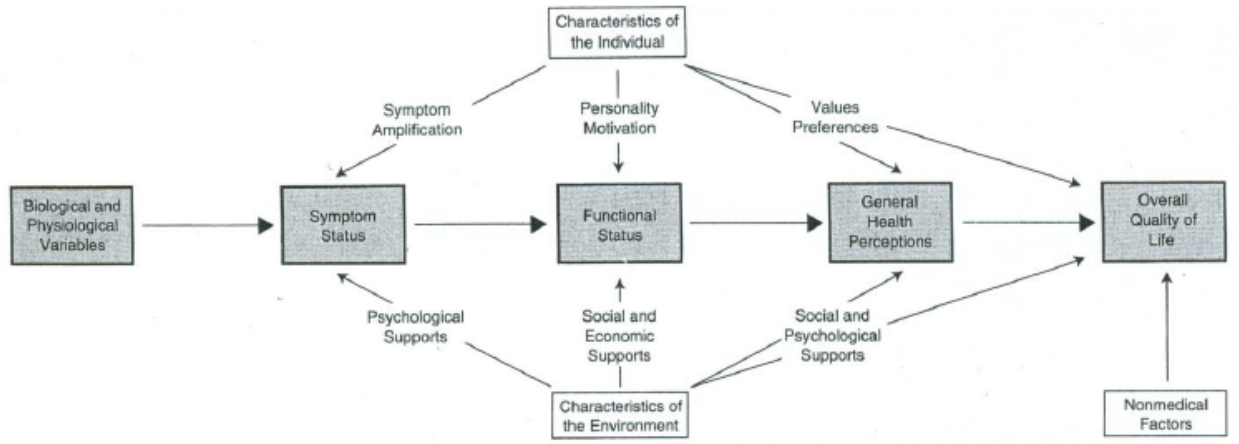

Figure 1. Wilson and Cleary's health-related quality of life framework[14]

4. PARTICIPANT RECRUITMENT

4.1 Study Setting

Children's Hospital of Philadelphia (CHOP) served as the coordinating center for the study. CHOP study staff provided a summary of the study's purpose and methods to coordinators and clinicians at the 20 sites that enrolled the most participants in the Chronic Kidney Disease in Children (CKiD) study, a longitudinal cohort study that began in 2005 with 56 sites in the United States and Canada.[15] Fifteen CKiD sites across the United States and one clinic in Canada chose to participate in the study. After practices completed the necessary training, obtained institutional review board approval, and executed a contract with CHOP, they were considered to be activated and allowed to begin participant recruitment. Activated practices received a $3,000 stipend and an additional $300 for each parent-child dyad enrolled from their site.

4.2 Participant inclusion criteria

Inclusion criteria for child participants were (1) aged 8 to <21 years of age at the time of enrollment, (2) able to self-report in English, (3) seen by a nephrologist within the past two years, (4) not receiving dialysis and no kidney transplant at time of enrollment, and (5) evidence of CKD, as defined by two eGFR readings of 6-89 ml/min at least three months apart, computed using the CKiD bedside estimating equation, which is based on a child's height and creatinine level.[16] Parent participants were English-speaking parents or legal guardians of the child participants.

4.3 Recruitment procedures

Recruitment took place from June 2017 to August 2018. Based on estimates of the number of eligible patients across participating sites, investigators determined that a feasible enrollment goal would be 180 (minimum) to 216 (maximum) parent-child dyads.[1] The CKiD coordinating centers at Children's Mercy Hospital and CHOP provided site coordinators with lists of eligible patients. Staff at two sites (CHOP and Cincinnati Children's Hospital Medical Center) searched nephrology clinic records to identify additional patients (not enrolled in CKiD) at their sites that met inclusionary criteria[2]. CKiD site coordinators sent recruitment letters or emails to the

[1] The expectation was a 50% enrollment rate of eligible CKiD patients and 75% for high-performing sites.
[2] This was a PEDSnet search using the inclusion criteria listed in section 4.2.

families of 121 CKiD participants who met inclusion criteria and followed up by phone or in person during clinic visits. CHOP study staff attempted to contact families of an additional 440 patients by mail, email, or phone. No more than three contact attempts were made for each family. Fifteen families declined the study when they were contacted. An additional 55 families expressed interest and were sent study materials but did not complete enrollment. A total of 212 parent-child dyads (90 CKiD and 122 non-CKiD) agreed to participate and were enrolled in the study.

5. DATA COLLECTION

5.1 Study design

The study design was a prospective cohort study with baseline and six follow-up assessments administered over the course of two years. Follow-up assessments were scheduled to occur within a four-week window of the following post-baseline timepoints: 3 months, 6 months, 12 months, 15 months, 18 months, 24 months. Participants 18 years or older provided informed consent, and children 8-17 years old provided assent. CHOP Institutional Review Board reviewed and approved study procedures (protocol number 17-013723). Parent-child dyads who consented to participate completed paper questionnaires or electronic questionnaires administered online with REDCap.

5.2 Questionnaires

At study baseline, parents completed screener questions to confirm study eligibility and then provided contact information, communication preferences, and sociodemographic information about themselves and their children. No dyads were deemed ineligible as a result of the screener questions. At each survey administration, parents and children completed PROMIS measures selected by pediatric nephrologists and measurement experts to assess the health and well-being of children with CKD. Parents completed the following PROMIS Parent Proxy short forms: Global Health 7 v1.0,[17] Family Relationships 4a v1.0,[18] Positive Affect 4a v1.0,[19] Depressive Symptoms v2.0 (4 items), and Anxiety v2.0 (4 items).[20] Items for the Depressive Symptoms short form were selected to match those included in the PROMIS Profile 25, and items for the Anxiety short form were selected to match items included in a concurrent study focused on validation of the PROMIS Pediatric sleep measures (Meltzer et al., 2019). Children completed the following PROMIS Pediatric short forms: Fatigue v2.0 (8 items),[21] Sleep Disturbance v1.0 (8 items), Sleep-related Impairment v1.0 (4 items),[22] Psychological Stress Experiences 4a v1.0,[23] Life Satisfaction 8b v1.0,[24] and Meaning and Purpose 4a v1.0.[25] Items for the Fatigue, Sleep Disturbance, and Sleep-related Impairment short forms were selected based on prior qualitative research with children with CKD (Forrest et al., 2020). The Meaning and Purpose short form was administered to children over the age of 12 because these items were deemed most relevant to adolescents rather than young children.

5.3 Retention and engagement

CHOP staff conducted a literature review and phone interviews with members of CHOP's Family Advisory Council to identify best practices for retention. One major theme was the need for systematic communication with participants, which was incorporated using the following strategies: (1) the creation of a tracking database that includes all contact information (updated frequently);[26-28] (2) a plan for identifying "at-risk" participants and using alternative means of

communication;[27, 28] and (3) a communication plan that outlines when participants are contacted, how often, and the messaging for each communication.[27, 28] CHOP staff used participants' preferred method of communication (mail, email, or text) to send follow-up questionnaires 14 days prior to the scheduled follow-up date and reminders (if the questionnaire was not completed) 10 days and 6 days prior to the follow-up date. If participants did not respond to their preferred method of communication, alternative methods of communication were used (mail, email, text, or phone calls). Contacts occurred no more than five times per week during the follow-up window.

Another theme was the need for establishing relationships with participants, which was incorporated in the study in the following ways: (1) acknowledging participants' contributions in "thank you" messages;[26] (2) providing monetary incentives that increased during critical data collection points;[28, 29] (3) providing non-financial tokens of appreciation (i.e., birthday cards);[28] and (4) maintaining a study web page and mailing a quarterly newsletter that informed participants about the study team and purpose of the project.[28] Parent and child participants each received a $35 gift card after completing the 12-month and 24-month questionnaires and each received a $20 gift card after completing the other questionnaires. In addition, social media sites are increasingly being used by online research panels and in longitudinal studies to improve recruitment and retention rates.[30, 31] Participants in this study were invited to join study-specific social media pages (i.e., Facebook and Instagram) with content relevant to the study and CKD.

5.4 Clinical data collection

CHOP staff extracted data for a number of clinical variables for the child participants. Clinical data for children enrolled in the CKiD study (n = 90) were extracted from the registry maintained by the CKiD data coordinating center at Johns Hopkins University using encrypted identifiers for study participants. To link participants' clinical data to their questionnaire data, CKiD site coordinators provided CHOP staff the identifiers associated with participants' names via secure data transmissions. Clinical data for all other child participants (n = 122) were extracted by reviewing their electronic health records. Data were collected from clinic visits that occurred within 12 months before and 24 months after each dyad's study baseline date.

6. PROMIS Scores

PROMIS measures were scored using R code from the Firestar program.[32] Firestar implements the Bayesian Expected A Posteriori (EAP) estimation procedure, which used the item parameters from IRT models reported in the literature and accounted for the pattern of responses on each item.[33] For each individual, this procedure results in a score that estimates the person's level on the underlying trait (e.g., severity of sleep disturbances) and the corresponding standard error of measurement of that score. Scores were converted to the PROMIS T-scale, which has a mean of 50 and standard deviation of 10. PROMIS measures are scored in the direction of their name. For example, better health is associated with higher Global Health scores and lower Fatigue scores.

7. REFERENCES

1) Selewski DT, Massengill SF, Troost JP, et al. Gaining the Patient Reported Outcomes Measurement Information System (PROMIS) perspective in chronic kidney disease: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol.* 2014;29(12):2347-2356.
2) DeWalt DA, Gross HE, Gipson DS, et al. PROMIS pediatric self-report scales distinguish subgroups of children within and across six common pediatric chronic health conditions. *Qual Life Res.* 2015.
3) Furth, S. L., Abraham, A. G., Jerry-Fluker, J., Schwartz, G. J., Benfield, M., Kaskel, F., ... & Warady, B. A. (2011). Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clinical Journal of the American Society of Nephrology*, *6*(9), 2132-2140.
4) National Research Council. *Subjective Well-Being: Measuring Happiness, Suffering, and Other Dimensions of Experience.* Washington, DC: The National Academies Press.; 2013.
5) Roumelioti ME, Wentz A, Schneider MF, et al. Sleep and fatigue symptoms in children and adolescents with CKD: a cross-sectional analysis from the chronic kidney disease in children (CKiD) study. *Am J Kidney Dis.* 2010;55(2):269-280.
6) Kogon AJ, Vander Stoep A, Weiss NS, Smith J, Flynn JT, McCauley E. Depression and its associated factors in pediatric chronic kidney disease. *Pediatr Nephrol.* 2013;28(9):1855-1861.
7) Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW. Health-related quality of life in pediatric patients with ESRD. *Pediatr Nephrol.* 2006;21(6):846-850.
8) McKenna AM, Keating LE, Vigneux A, Stevens S, Williams A, Geary DF. Quality of life in children with chronic kidney disease-patient and caregiver assessments. *Nephrol Dial Transplant.* 2006;21(7):1899-1905.
9) Riano-Galan I, Malaga S, Rajmil L, et al. Quality of life of adolescents with end-stage renal disease and kidney transplant. *Pediatr Nephrol.* 2009;24(8):1561-1568.
10) Gere J, Schimmack U. A multi-occasion multi-rater model of affective dispositions and affective well-being. *Journal of Happiness Studies.* 2011;12(6):931-945.
11) Goldstein SL, Rosburg NM, Warady BA, et al. Pediatric end stage renal disease health-related quality of life differs by modality: a PedsQL ESRD analysis. *Pediatr Nephrol.* 2009;24(8):1553-1560.
12) DeWalt DA, Gross HE, Gipson DS, et al. PROMIS pediatric self-report scales distinguish subgroups of children within and across six common pediatric chronic health conditions. *Qual Life Res.* 2015.
13) Selewski DT, Massengill SF, Troost JP, et al. Gaining the Patient Reported Outcomes Measurement Information System (PROMIS) perspective in chronic kidney disease: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol.* 2014;29(12):2347-2356.
14) Wilson, I. B., & Cleary, P. D. (1995). Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. *JAMA*, *273*(1), 59-65.
15) Furth, S. L., Cole, S. R., Moxey-Mims, M., Kaskel, F., Mak, R., Schwartz, G., ... & Warady, B. A. (2006). Design and methods of the Chronic Kidney Disease in Children

(CKiD) prospective cohort study. *Clinical Journal of the American Society of Nephrology*, *1*(5), 1006-1015.
16) Schwartz, G. J., Munoz, A., Schneider, M. F., Mak, R. H., Kaskel, F., Warady, B. A., & Furth, S. L. (2009). New equations to estimate GFR in children with CKD. *Journal of the American Society of Nephrology*, *20*(3), 629-637.
17) Forrest, C. B., Bevans, K. B., Pratiwadi, R., Moon, J., Teneralli, R. E., Minton, J. M., & Tucker, C. A. (2014). Development of the PROMIS® pediatric global health (PGH-7) measure. *Quality of Life Research*, *23*(4), 1221-1231.
18) Bevans, K. B., Riley, A. W., Landgraf, J. M., Carle, A. C., Teneralli, R. E., Fiese, B. H., ... & Forrest, C. B. (2017). Children's family experiences: development of the PROMIS® pediatric family relationships measures. *Quality of Life Research*, *26*(11), 3011-3023.
19) Forrest, C. B., Ravens-Sieberer, U., Devine, J., Becker, B. D., Teneralli, R. E., Moon, J., ... & Bevans, K. B. (2018). Development and evaluation of the PROMIS® pediatric positive affect item bank, child-report and parent-proxy editions. *Journal of happiness studies*, *19*(3), 699-718.
20) Varni, J. W., Thissen, D., Stucky, B. D., Liu, Y., Gorder, H., Irwin, D. E., ... & DeWalt, D. A. (2012). PROMIS® Parent Proxy Report Scales: an item response theory analysis of the parent proxy report item banks. *Quality of Life Research*, *21*(7), 1223-1240.
21) Lai, J. S., Stucky, B. D., Thissen, D., Varni, J. W., DeWitt, E. M., Irwin, D. E., ... & DeWalt, D. A. (2013). Development and psychometric properties of the PROMIS® pediatric fatigue item banks. *Quality of Life Research*, *22*(9), 2417-2427.
22) Forrest, C. B., Meltzer, L. J., Marcus, C. L., de la Motte, A., Kratchman, A., Buysse, D. J., ... & Bevans, K. B. (2018). Development and validation of the PROMIS Pediatric Sleep Disturbance and Sleep-Related Impairment item banks. *Sleep*, *41*(6), zsy054.
23) Bevans, K. B., Gardner, W., Pajer, K. A., Becker, B., Carle, A., Tucker, C. A., & Forrest, C. B. (2018). Psychometric evaluation of the PROMIS® pediatric psychological and physical stress experiences measures. *Journal of pediatric psychology*, *43*(6), 678-692.
24) Forrest, C. B., Devine, J., Bevans, K. B., Becker, B. D., Carle, A. C., Teneralli, R. E., ... & Ravens-Sieberer, U. (2018). Development and psychometric evaluation of the PROMIS Pediatric Life Satisfaction item banks, child-report, and parent-proxy editions. *Quality of Life Research*, *27*(1), 217-234.
25) Ravens-Sieberer, U., Devine, J., Bevans, K., Riley, A. W., Moon, J., Salsman, J. M., & Forrest, C. B. (2014). Subjective well-being measures for children were developed within the PROMIS project: presentation of first results. *Journal of clinical epidemiology*, *67*(2), 207-218.
26) Tansey CM, Matte AL, Needham D, & Herridge MS (2007). Review of retention strategies in longitudinal studies and application to follow-up of ICU survivors. *Intensive Care Medicine*, 33: 2051-2057.
27) Meneses K & Roche C (2009). Recruitment and Retention in Clinical Research. *Perioperative Nursing Clinics*, 4(2009) 259-268.
28) Abshire M, Dinglas VD, Cajita MIA, Eakin MN, Needham, DM, & Dennison Himmelfarb C (2017). Participant retention practices in longitudinal clinical research studies with high retention rates, *BMC Medical Research Methodology*, 17:30.
29) Van Wijk E (2014). Recruitment and Retention of Vulnerable Populations: Lessons Learned from a Longitudinal Qualitative Study. *TQR*, 19 (28).
30) Farina-Henry E, Waterston LB, & Blaisdell LL. Social media use in research: Engaging

communities in cohort studies to support recruitment and retention. *JMIR Research Protocols*. Sep 2015; 4 (3): e90.
31) Mychasiuk R & Benzies K. Facebook: An effective tool for participant retention in longitudinal research. Child: Care, health and development. Oct 2011; 38 (5): 753-756.
32) Choi, S. W. (2009). Firestar: Computerized adaptive testing simulation program for polytomous item response theory models. *Applied Psychological Measurement*, *33*(8), 644.
33) Bock, R. D., & Mislevy, R. J. (1982). Adaptive EAP estimation of ability in a microcomputer environment. *Applied psychological measurement*, *6*(4), 431-444.