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Preparation and Rationale for a Patient-Centered Clinical Outcome Assessment Set of Fluid Overload for Drug Development in Nephrotic Syndrome

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Keywords
Prepare-NS rationale · Systematic review · Gap analysis and design manuscript · Patient-reported outcomes

Abstract
Introduction: Fluid overload is a source of substantial morbidity for adults and children with nephrotic syndrome (NS). Preparation and Rationale for a Fluid Overload in Nephrotic Syndrome Clinical Outcomes Assessment Set for Drug Development (Prepare-NS, 5UG3FD007308) was funded by the US Food and Drug Administration to develop a core set of patient-reported and observer-reported (for young children) outcome measures of fluid overload for use in pharmaceutical trials across the lifespan. ***Methods:*** The Prepare-NS study team developed the proposed context of use with input from stakeholders. We conducted a scoping review to assess the available literature on relevant patient- and observer-reported measures and performed secondary analyses of existing qualitative and quantitative data. ***Results:*** The outcome set will aim to serve individuals 2 years of age and older with primary NS conditions (specifically focal segmental glomerulosclerosis, minimal change disease, IgM nephropathy, membranous nephropathy, and childhood-onset NS not biopsied). The existing literature describing patient-reported outcomes in NS largely relies on nonspecific measures of health-related quality of life; fluid overload has been associated with lower scores on these measures. ***Conclusion:*** To address the gap in measure availability and fluid overload content, the Prepare-NS team has launched a set of qualitative studies for concept elicitation from the population of interest to

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inform development of new measures. The resulting measures subsequently will undergo psychometric evaluation and validation in a survey study.

Introduction

Nephrotic syndrome (NS) results from rare kidney diseases that affect both children and adults. In this condition, fluid overload (FO) can significantly impede one's health-related quality of life (HRQoL). A recent international Delphi survey of 734 individuals with glomerular disease (inclusive of NS) or their caregivers from 59 countries found that 85 percent of respondents considered FO critically important [1]. One conceptual model to capture the many potential impacts of FO is shown in Figure 1. The absence of a set of clinical outcome assessments (COAs) addressing FO in NS, such as patient-reported outcomes (PROs), observer-reported outcomes (ObsROs), or performance outcomes that are fit for drug development purposes, is a barrier to the inclusion of patient-prioritized clinical trial endpoints.

The need for expansion of patient-centered COA endpoints within trials has been highlighted in the glomerular disease literature [2]. A 2017 review of the range of outcomes reported in randomized trials of pediatric chronic kidney disease (of which children with NS are a subset) found PROs were particularly lacking. Specifically, among 205 trials reporting 5,776 different outcomes, only 10% of these outcomes were measures of HRQoL as reported by either parent proxies or patients [3]. The dearth of trials with COA endpoints is not unique to kidney disease, prompting the US Food and Drug Administration (FDA) to place increased emphasis on patient-focused drug development [4], including establishment of a pilot grant program supporting the creation of publicly available sets of COAs [5]. Through this mechanism, *Preparation and Rationale for a Fluid Overload in Nephrotic Syndrome Clinical Outcomes Assessment Set for Drug Development* (Prepare-NS, 5UG3FD007308) was funded to develop a core set of FO COAs for use in NS trials across the lifespan. This paper describes the results of our approach to define the context of use for the new COA set, assess the current state of evidence and measure resources, and outline our study design to complete COA measure development and validation for FO in NS.

Methods

Context of Use

The Prepare-NS study team developed the proposed context of use inclusive of patient age and kidney diagnoses with input from Stakeholder Engagement Group, Clinician Expert Panel, External Technical Advisory Panel advisory groups. Endorsement from representatives of the FDA was the required final step in defining the context of use of the proposed COA measures.

Scoping Review of Literature

We conducted a scoping review to assess the available literature on PRO/ObsRO measures and data focused on the NS population. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) offers an extension for scoping reviews (PRISMA-ScR) [6]. Using the PRISMA approach, we developed a formal protocol on which the FDA program team provided feedback. Led by the informaticist (EC), we conducted electronic searches of PubMed, Embase, Cochrane Central, Scopus, and Google Scholar with restrictions for English language and human studies from January 1, 1990 to present. Search terms were generated to include the concepts of NS and associated kidney diseases, FO, and patient-reported or observer-reported measures (see Table 1 for complete list of search terms and operators).

A preliminary conceptual model was developed based on this scoping review with input from expert advisors. Furthermore, an inventory of existing measures was generated from the literature review and expanded with measures known to the Prepare-NS study team and assembled advisory groups. Measures and items were then reviewed to assess their population focus, e.g., general population, NS, or specific kidney diseases; inclusion of content related to edema or FO; respondent type. We used the results of the scoping review to identify gaps in available COAs fit for purpose to include in NS trial endpoints.

Qualitative Data Review and Analysis

A summary of the published qualitative studies was generated from the scoping literature review. In addition, a secondary thematic content analysis of existing qualitative data from a previously published interview guide [7] was conducted to examine both lifetime experience of edema for children and adults with focal segmental glomerulosclerosis (FSGS), as well as children and adults with minimal change disease (MCD). Latent content analysis also was used to

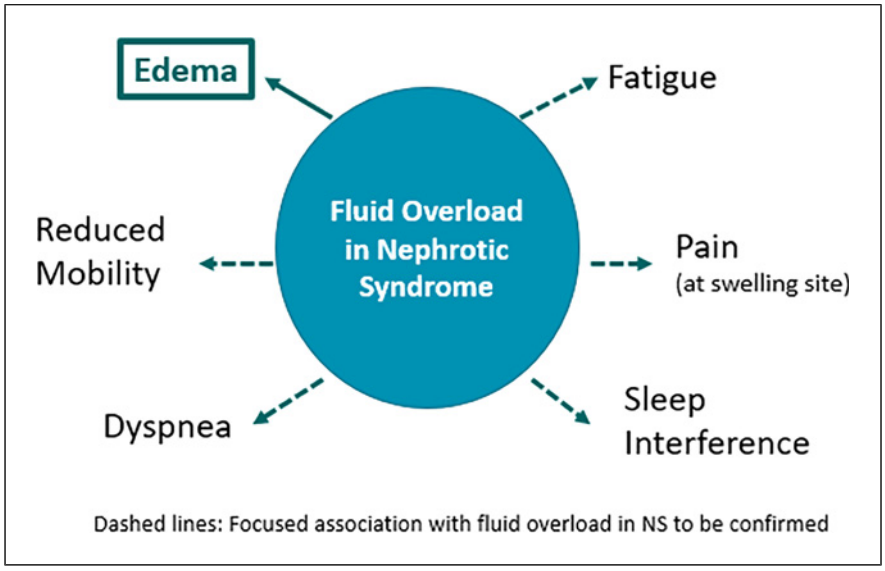

Fig. 1. Conceptual model reflecting potential impacts of FO in NS.

generate a summary of the overall frequencies and percentages of individuals that reported swelling for different body parts. Frequencies were examined for the full sample, separately for FSGS and MCD, and separately for both children and adults (see online suppl. materials; for all online suppl. material, see https://doi.org/10.1159/000539921).

Quantitative Data Analysis

We performed quantitative analyses to help identify the most burdensome symptoms associated with edema among NS patients. Existing data from two NIH-sponsored prospective observational studies were included in secondary analyses. The Nephrotic Syndrome Study Network (NEPTUNE; U54DK083912) is a prospective observational cohort of over 700 children and adults (USA and Canada) with incident FSGS, MCD, MN, childhood-onset NS, and other conditions [8]. The Cure Glomerulopathy Network (CureGN) is a prospective observational cohort of over 2,400 children and adults throughout the USA, Canada, and Europe enrolled with prevalent MCD, FSGS, MN, and IgA nephropathy [9]. In both the NEPTUNE and CureGN datasets, measures from the Patient-Reported Outcomes Measurement Information System® (PROMIS®) domains were administered. For each domain, we considered differences of ≥3 points as clinically relevant for consideration in future COA development [10]. For the child cohort, the Pediatric Quality of Life Inventory (PedsQL)8–12 and PedsQL13-18 instruments also were administered. We summarized patient characteristics and estimated mean differences in symptom burden and HRQoL between patients with and without edema, stratified by age group. Here, 95% confidence intervals (CIs) were calculated for the mean differences. A 95% CI crossing 0 indicated that the difference was not statistically significant. In addition, we examined whether the point estimate exceeded thresholds for important differences.

Ethics

IRB approval was obtained prior to the commencement of the secondary data analyses by the Institutional Review Board at the University of Michigan (HUM00208148). Individuals 18 and older, and parents/guardians of individuals younger than 18, provided written informed consent at enrollment for both NEPTUNE and CureGN.

Results

Context of Use

With input from advisory committees and the FDA, the Prepare-NS COAs will aim to serve a population that is (1) age 2 years (24 months) and older with (2) primary NS conditions (specifically FSGS, MCD, IgM nephropathy, membranous nephropathy, and childhood-onset NS not biopsied) and (3) persistent or relapsing and remitting NS with nephrotic range proteinuria and edema at (4) any stage of chronic kidney disease, excluding dialysis-dependent populations. The context of use helps establish the scope for our COA core set, which is depicted in Figure 2. In this model, we demonstrate the

Table 1. Search terms for literature review to establish existing patient and observer outcomes related to FO

Include	Exclude
See "Search strategy" below	Article not in English
	Opinion/conceptual models/absent data
	Case studies
	Animal studies
	Conference abstracts
	Dialysis
	Inflammatory disorders (e.g., lupus, ANCA vasculitis)

#	Search strategy
Search strategy – sample from PubMed database	
1	"nephrotic syndrome*"[tw] OR "Nephrotic syndrome"[Mesh]
2	"minimal change disease"[tw] OR "Nephrosis, Lipoid"[Mesh]
3	"focal segmental glomerulosclerosis"[tw] OR FSGS[tw] OR "Glomerulosclerosis, Focal Segmental"[Mesh]
4	"membranous nephropathy"[tw] OR "Glomerulonephritis, Membranous"[Mesh]
5	"steroid sensitive nephrotic syndrome"[tw] OR "steroid resistant nephrotic syndrome"[tw] OR "steroid-responsive nephrotic syndrome"[tw] OR SRNS[tw] OR "steroid dependent nephrotic syndrome"[tw] OR "Steroid dependent idiopathic nephrotic syndrome"[tw]
6	"C3 glomerulopathy"[tw] OR "idiopathic membranoproliferative glomerulonephritis"[tw] OR C3GN [tw] OR C3G[tw] OR DDD[tw]
7	"IgA nephropathy"[tw] OR "Immunoglobulin A Nephropathy"[tw] OR "IGA glomerulonephritides"[tw] OR "IGA glomerulonephritis"[tw] OR "Glomerulonephritis, IGA"[Mesh]
8	("kidney transplant*"[tw] OR "Kidney Transplantation"[MeSH]) AND ("FSGS recurrence"[tw] OR "C3GN recurrence"[tw] OR "C3G recurrence"[tw] OR "DDD recurrence"[tw])
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	Swell*[tw] OR edema[tw] OR "Edema"[Mesh]
11	"fluid overload"[tw] OR "fluid mmobilee*"[tw] OR "fluid retent*"[tw]
12	hypervolemi*[tw]
13	anasarca*[tw]
14	ascites [tw] OR "Ascites"[Mesh]
15	#10 OR #11 OR #12 OR #13 OR #14
16	#9 AND #15
17	"patient reported outcome*"[tw] OR "self-reported outcome*"[tw] OR (PROs[tw] AND outcome*[tw]) OR "quality of life"[tw] OR QOL[tw] OR "Patient Reported Outcome Measures"[Mesh] OR "Quality of Life"[Mesh]
18	"observer reported outcome*"[tw]
19	"clinician reported outcome*"[tw] OR "physician reported outcome*"[tw] OR "nurse reported outcome*"[tw] OR "pharmacist reported outcome*"[tw] OR PhROs[tw][1]
20	Questionnaire[tw] OR survey[tw] OR instrument[tw] OR tool[tw] OR "Surveys and Questionnaires"[Mesh]
21	#17 OR #18 OR #19 OR #20
22	"weight gain"[tw] OR "Weight Gain"[Mesh]

Table 1 (continued)

23	"shortness of breath"[tw] OR dyspnea[tw] OR "Dyspnea"[Mesh]
24	"exercise intolerance"[tw] OR "exercise tolerance"[tw] OR "exercise capacity"[tw] OR mmobil*[tw] OR "Exercise Tolerance"[Mesh] OR "Fatigue"[Mesh]
25	Discomfort[tw] OR pain[tw] OR "Pain"[Mesh]
26	Mobil*[tw] OR mmobile*[tw] OR "difficulty walking"[tw] OR "walking difficult*"[tw] OR "ambulatory difficult*"[tw] OR "ambulation difficult*"[tw] OR "difficulty ambulat*"[tw] OR "Mobility Limitation"[Mesh]
27	#22 OR #23 OR #24 OR #25 OR #26
28	#21 OR #27
29	#9 AND #15 AND #28
#30	#29 AND ("1990/01/01"[PDAT]: "3000/12/31"[PDAT])

[1]At time of initial protocol submission, ClinROs were included in the scoping review.

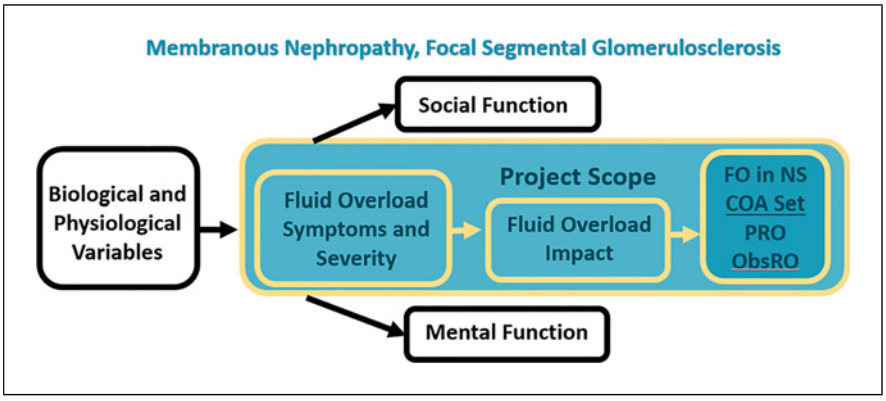

Fig. 2. Project scope for Prepare-NS. NS, nephrotic syndrome; FO, fluid overload; COA, clinical outcome assessment; PRO, patient-reported outcome, ObsRO, observer-reported outcome.

requirement to focus on FO and the impact that FO has on the physical functioning of children and adults with NS. While published literature highlights the importance of emotional and social health to patients, these domains are excluded here to retain the focus on domains that are reasonably likely to change as a direct result of disease-modifying therapy.

Literature Review

Results from the scoping literature review are summarized in the PRISMA diagram in Figure 3. Our initial search strategy yielded 1,337 unique records. After title and abstract screening (ES and RS), 174 abstracts were identified for full-text review. Conflicts about inclusion/exclusion determination were resolved through discussion with the larger study team. A total of nine studies met eligibility criteria. Additional seven articles were captured in the supplemental search of clinical trials.

Existing Measures

A summary of existing PRO measures used in NS research is presented in Table 2. The PRO literature in NS largely relies on nonspecific measures of HRQOL; FO has been associated with lower scores on these measures [11–14]. Questions in these measures rarely assessed FO/edema directly but did assess symptoms that can result from edema in our conceptual model, such as fatigue and physical functioning. In addition, we identified three examples of disease-specific PROs developed for a subset of the selected NS diagnoses in the Prepare-NS context of use, namely, FSGS and MCD. A subgroup of our Prepare-NS team participated in or was responsible for the development of each identified measure in previous projects. An independent review of identified PROs was conducted by Prepare-NS team members not involved in their development to mitigate potential bias. The review included (1) the measures themselves; (2) related publications [15]; (3) technical summaries; and (4) concept elicitation interview guides.

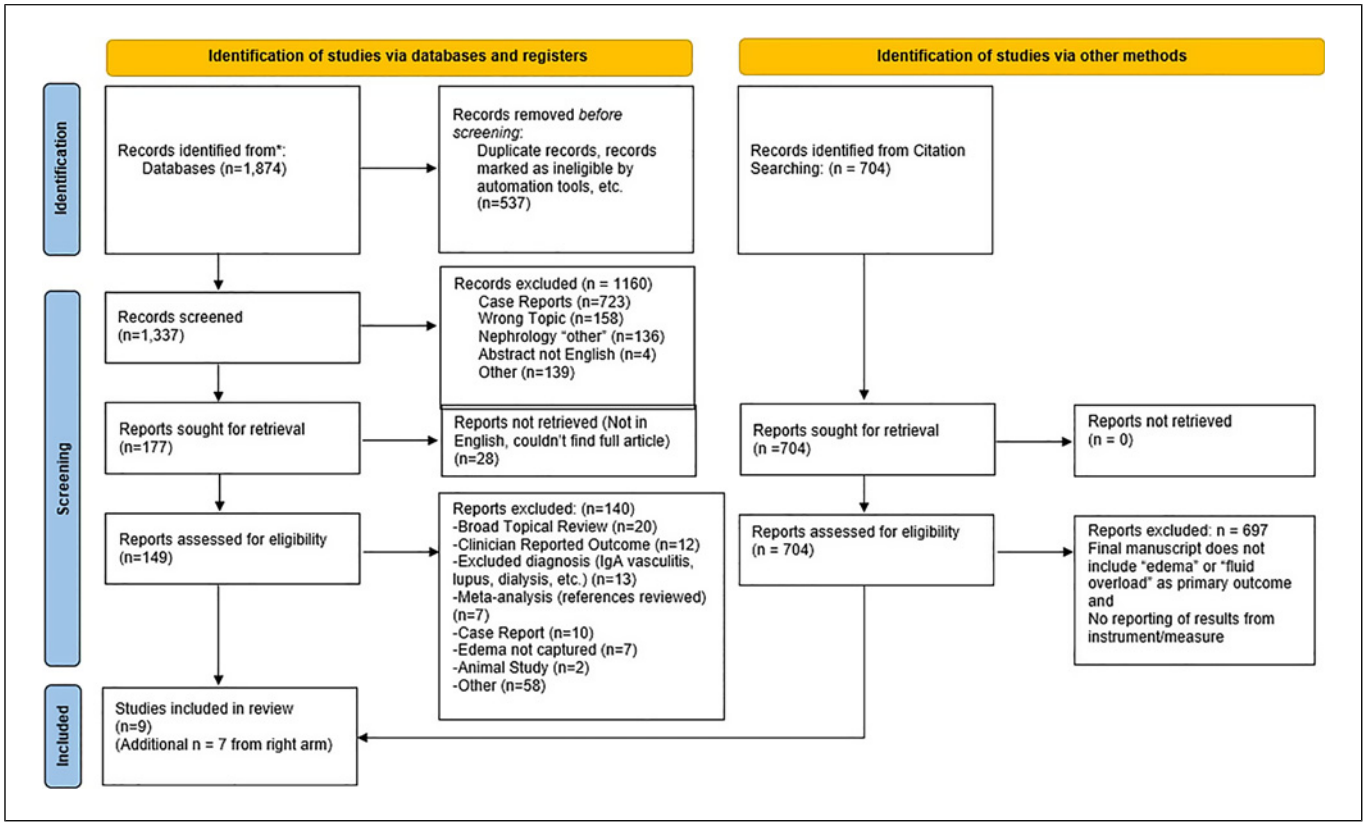

Fig. 3. PRISMA flow diagram summarizing results from the scoping literature review. Search terms were generated to include the concepts of NS, FO/edema, and patient-reported or observer-reported measures. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

FSGS Symptom Diary and the FSGS Symptom Impact Questionnaire

Two PROs relating to one of our NS diagnoses, the FSGS symptom Diary and the FSGS Symptom Impact Questionnaire, utilize 43 items to cultivate a complete assessment of symptoms and how they can impact adults with FSGS. For the development of these measures, participants engaged in concept elicitation and cognitive debriefing interviews to ensure relevancy, comprehensiveness, and understandability for each item [15]. Interview guides received input from clinical advisors to ensure consistency with clinical experiences. Concept elicitation findings, a review of literature, and input from clinical advisors constitute the sources for PRO drafting.

FSGS-MCD PRO

The FSGS-MCD PRO was developed to meet the need for a multidimensional disease-specific PRO for use in the pediatric and adult population affected by either FSGS or MCD. Adapted from the Adult FSGS PRO, it includes additional data collected from children and adults with FSGS, as well as both children and adults with MCD [7]. Similar to the development of the FSGS Symptom Diary and the FSGS Symptom Impact Questionnaire for adults, and in concordance with the FDA guidance for PRO development, the FSGS-MCD PRO was developed using findings from a literature review, qualitative interviews, and expert review to identify and characterize salient domains of HRQOL that are important to children and adults with FSGS and MCD. The resultant PRO is relevant for individuals aged 8 years or older with either FSGS or MCD. It includes both generic and FSGS-MCD disease-specific contents and has undergone readability and translatability reviews.

These disease-specific PRO measures assess edema severity and location but do not explicitly assess the impact of edema or FO on how a patient feels or functions. We note that major PRO measurement systems like the NIH PROMIS® capture relevant impacts of NS-associated edema, such as fatigue and physical function, but not with attribution to edema [14, 16]. No

Table 2. Existing PROs and ObsROs relevant to NS

PROs with direct measures of edema	
FSGS Symptom Impact Questionnaire	
FSGS Symptom Diary	
FSGS-MCD PRO	
PROs and ObsROs without direct measures of edema (items/domains possibly impacted by edema listed below each measure)	
Achenbach Child Behavior Checklist	
• None	
EuroQOL	
• "I have no/some/a lot of problems walking about"	
• "I have no/some/a lot of problems washing or dressing myself"	
• "I have no/some/a lot of problems doing by usual activities"	
• "I have no/some/a lot of pain or discomfort"	
KINDL	
Child-reported outcomes	*ObsROs*
• "I was tired and worn-out"	• "My child romped around and was very active"
• "I played with friends"	• "My child was lively and energetic"
	• "My child complained of being in pain"
PedsQL	
• Physical functioning	
PROMIS	
• Adult: global assessment, physical function, fatigue, pain interference, sleep	
• Child: mobility, fatigue, pain	
SDQ	
• "Often complains of headaches, stomachaches, or sickness"	
Medical Outcomes Study Questionnaire SF36	
• "[Various activities] limited a lot/limited a little/not limited at all"	
• "Work limitations/difficulties – yes/no"	
• "How much bodily pain have you had during the past 4 weeks?"	
• "Did you feel full of pep?"	
• "Did you have a lot of energy?"	
• "Did you feel tired?"	
• "How much of the time has your physical health or emotional problems interfered with you social activities?"	

FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; PRO, patient-reported outcome; ObsRO, observer-reported outcome; PedsQL, Pediatric Quality of Life Inventory; SDQ, Strengths and Difficulties Questionnaire; SF36, Short Form 36.

disease-specific PRO measures were identified for membranous nephropathy or child-onset NS. Furthermore, we were unable to find any measures addressing edema or FO in NS for children too young to self-report. We note that proxy measures are not permissible for use as COAs for the purposes of drug development. Our consideration of previous measures is ultimately limited by evaluation of existing measures and data that are within the approved context of use in the project. Our focus will remain limited to edema and FO resulting from NS.

Qualitative Study

Published qualitative data informing the development of the FSGS-MCD PRO identified several key physical symptoms and HRQOL domains [7]. Reporting percentages of a combined sample of children and adults with FSGS and MCD (N = 48), the following physical symptoms were identified: swelling (92%), pain (88%), problems with sleep (88%), fatigue (83%), changes in appetite (81%), mobility impairment (75%), changes in appearance (73%), problems performing activities of daily living, including instrumental activities of daily

Table 3. Characteristics of pooled CureGN and NEPTUNE participants with PROMIS measures

	Adult (*N* = 1,246)	Child (*N* = 432)
Edema at PROMIS assessment, *n* (%)		
No	101 (8)	101 (23)
Yes	1,142 (92)	325 (75)
Unknown/missing	3 (0)	6 (1)
Age at PROMIS assessment, median (IQR), years	48 (32, 60)	11 (8, 14)
Time from entry to PROMIS assessment, median (IQR), months	0 (0, 1)	2 (0, 19)
Sex, *n* (%)		
Male	674 (54)	225 (52)
Female	572 (46)	207 (48)
Race, *n* (%)		
Asian/Asian American	21 (2)	11 (3)
Black/African American	251 (20)	127 (29)
Native American/Alaskan Native/First Nation	71 (6)	13 (3)
Native Hawaiian/Other Pacific Islander	10 (1)	7 (2)
White/Caucasian	829 (67)	228 (53)
Multiracial	22 (2)	27 (6)
Unknown/missing	42 (3)	19 (4)
Ethnicity, *n* (%)		
Hispanic or Latino	160 (13)	69 (16)
Not Hispanic or Latino	1,074 (86)	354 (82)
Unknown/missing	12 (1)	9 (2)
Diagnosis, *n* (%)		
MCD	272 (22)	228 (53)
FSGS	451 (36)	140 (32)
Membranous nephropathy	521 (42)	30 (7)
Childhood-onset NS not biopsied	2 (0)	34 (8)

IQR, interquartile range.

living (67%). We also note that complaints around mental health (i.e., anxiety, depression, positive well-being) and social health (i.e., social participation, social satisfaction) were common [7].

Published concept elicitation data informing the development of the FSGS Impact Questionnaire and Symptom Diary in adults alone identified patient-reported swelling in 100% of participants (*N* = 25) [15]. The most common locations of swelling were from the waist down, including legs, knees, ankles, and feet (80%); stomach/abdomen (52%); face, eyes, or skull (40%); arms, hands, or fingers (36%); and generalized swelling (i.e., all over the body) (20%). Other commonly reported FSGS symptoms were fatigue (68%); pain or pressure (36%); shortness of breath (24%); foamy/frothy urine (12%); headaches or shooting pains (12%); and depression (12%). The impacts of these symptoms were also described. A total of 52% of participants reported FSGS affected their ability to do physical activities. FSGS symptoms also affected sleep, with 47% reporting difficulty in falling asleep and 31% reporting waking up during the night. Finally, 31% described an impact on bathing, dressing, or eating.

From reassessment of existing transcripts of edema location in children 8 years or older (*n* = 22) and adults (*n* = 26) with either FSGS or MCD, we examined the frequency of patients endorsing swelling for a specific body part [11]. Over 90% of total participants reported some swelling. The most common areas of swelling were consistent with above findings. Patients with FSGS were most likely to describe ankle swelling, while patients with MCD most frequently endorsed abdomen or stomach swelling. The existing qualitative sources did not include content that explicitly addressed the attribution of functional impairment due to edema or direct impact of edema.

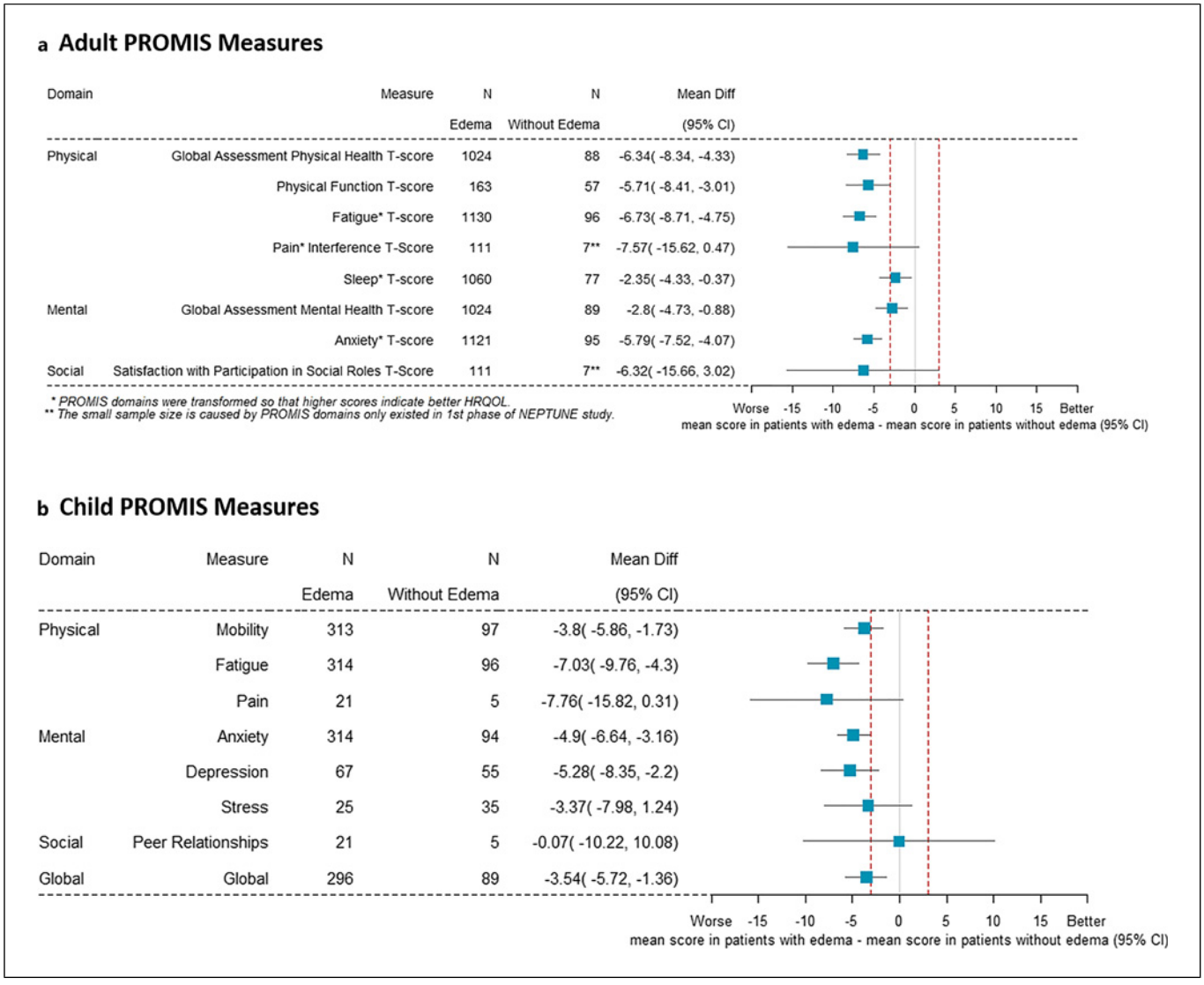

Fig. 4. a, **b** Comparison of HRQOL domain scores by edema status in adults and children with primary NS. Pooled responses to PROMIS measures from the NEPTUNE and CureGN cohorts.

Quantitative Data

Table 3 presents the NEPTUNE and CureGN participant characteristics included in this analysis. Comparisons of the general HRQoL domains, pooling the NEPTUNE and CureGN participant cohorts, with and without edema are shown in the forest plots in Figure 4, Panels A and B. The sample size for each measure varies because of late addition of specific PROMIS domains in the respective studies. For each, the mean difference reflects the mean score for patients with edema versus those without edema. Since all scores have been calculated so that higher scores indicate better health, a negative difference indicates worse symptoms or HRQOL for patients with edema. Among adults, the largest mean negative differences were observed for PROMIS domains of fatigue, global physical health, anxiety, and physical function. For these measures, the upper bounds of the 95% CI are less than −3 and thus indicate clinically relevant symptoms or quality of life domains for consideration in future COA development. The estimated mean negative differences for Pain Interference and Satisfaction with Participation in Social Roles and Activities were also of large magnitude, but the 95% CIs were wide, likely due to a small sample size of patients without edema for these measures (Panel A). Among children, the PROMIS scores with the largest mean negative differences were pain interference, fatigue, depression,

anxiety, global health, and mobility (Panel B). For pain interference, fatigue, depression, and anxiety measures, the upper bounds of the 95% CI are less than −3 and thus indicate clinically relevant symptoms or quality of life domains for consideration in future COA development.

Discussion

In 2021, we launched the Prepare-NS study with the overall goal of producing a set of PRO and ObsRO (family/caregiver) COAs focused on NS patients' experience of FO. Furthermore, the goal of these measures is to be fit for regulatory use, specifically drug development, across the severity and lifespan continuum. This COA set will be applicable to conditions associated with NS; they will assess FO, its contribution to symptom burden, and its impact on HRQoL with a focus on assessing concepts that are reasonably likely to be changed with an effective disease-modifying therapy.

Prepare-NS will develop COAs for FO by identifying and addressing several key gaps. First, the existing measures for self-responding children age 8 years and older and adults with FSGS or MCD do not focus on the issue of FO and its impact. Second, there is an absence of an ObsRO measure for the assessment of FO in young children. Third, concept elicitation is fully absent from adults and children with IgM nephropathy, membranous nephropathy, childhood-onset NS not biopsied, and NS recurrence in kidney transplant recipients. Fourth, current PROs were not developed with a focus on FO. Consequently, NS-related FO-specific concerns are not fully captured by existing measures. Finally, the differences seen in general HRQOL measures for both adults and children with edema highlight that the presence or absence of edema alone does not sufficiently capture individual experience; the new measure must also address downstream impacts of edema.

Next Steps

To address the gap in measure availability and FO in NS-specific content, the Prepare-NS team has launched a set of qualitative studies for concept elicitation from the full spectrum of respondents aligning with the defined context of use (NCT05505500). Information gathered from these interviews will inform FO in NS PRO and ObsRO measure development.

After developing initial versions of the FO PROs and ObsRO, we will include these instruments and anchor measures in a survey study for the purpose of psychometric evaluation. This study will recruit a cohort of NS patients and caregivers/parents covering the range of ages and NS diagnoses included in the context of use. Using these data, we will determine the ceiling/floor effects, internal consistency reliability, test-retest reliability, convergent validity, known-group validity, and responsiveness to change in health for the COAs. We also will define recommendation administration/scoring and identify thresholds for meaningful differences/changes that can be used to form endpoints for clinical trials.

Acknowledgment

The Prepare-NS team would like to thank Dr. Debbie Gipson for her essential contributions as previous mPI of Prepare-NS during her tenure at the University of Michigan.

Statement of Ethics

Participants 18 and older, and parents/guardians of participants younger than 18, in the NEPTUNE and CureGN cohort studies provided written informed consent at time of enrollment. Approval was obtained from the Institutional Review Board at the University of Michigan (HUM00208148) prior to the commencement of secondary data analyses of study data.

Conflict of Interest Statement

Eloise Salmon, Noelle E. Carlozzi, Jin-Shei Lai, Catherine Spino, Yujie Wang, Emily Capellari, Rebecca Scherr, Kayla Sifre, Shawn Sullivan, Courtney Hurt, Tina Creguer, Kelly Helm, Richard Lafayette, Patrick H. Nachman, David T. Selewski, and John Devin Peipert report no conflicts of interest.

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Author Contributions

Eloise Salmon contributed to investigation and writing (original draft, review, and editing). Noelle E. Carlozzi contributed to methodology, formal analysis, and writing (original draft, review, and editing). Jin-Shei Lai contributed to methodology, formal analysis, and writing (review and editing). Catherine Spino contributed to conceptualization, methodology, formal analysis, and writing (original draft, review, and editing). Yujie Wang contributed to formal analysis. Emily Capellari, Kelly Helm, Richard Lafayette, Patrick H. Nachman, and David Selewski contributed to methodology and investigation. Rebecca Scherr and Shawn Sullivan contributed to investigation. Kayla Sifre contributed to

writing (review and editing). Courtney Hurt and Tina Creguer contributed to project administration. John Devin Peipert contributed to conceptualization, methodology, formal analysis, writing (original draft, review, and editing), supervision, and funding acquisition.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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