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Prepare-NS Gap Analysis

Gap Analysis of Measures, Literature, Observational Data, and Qualitative Data Related to Nephrotic Syndrome

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1 BACKGROUND

As part of its UG3 study phase, the Prepare-NS team is developing and validating clinical outcome assessments (COAs) and endpoints fit for regulatory purpose in patients with nephrotic syndrome and fluid overload/edema. These COAs will assess fluid overload (FO) as patient-reported outcomes (PRO) and observer-reported outcomes (ObsRO).

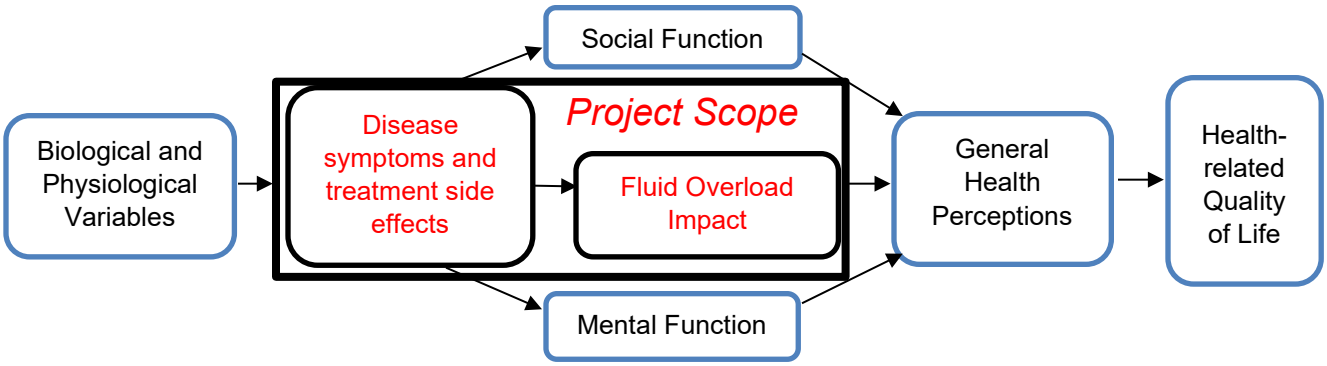
1.1 Nephrotic syndrome

Nephrotic syndrome (NS) is defined as a combination of abnormally elevated levels of protein in the urine, abnormally low levels of protein in the blood, and edema. NS is the manifestation of rare and common kidney diseases that affects children and adults and when uncontrolled leads to progressive kidney damage and kidney failure. Presently there is a profound unmet need in the availability of effective and safe therapies for NS associated conditions. Consequently, these diseases lead to poor health related quality of life (HRQOL) and are leading causes of end stage kidney disease in the United States.[1,2] While translational science is progressing with increasing numbers of drug development initiatives, the absence of a validated set of COAs fit for drug development purposes is a barrier to the inclusion of patient-centered endpoints in clinical trials.

1.2 Need for drug development in NS

FO in NS produces unwanted physical and emotional symptoms that often limit the ability of people to live fully functional lives. FO symptoms, such as edema, dyspnea, fatigue, pain and impaired mobility, are cross-cutting with symptoms and side effects that are common across multiple diseases. As such, it is a prime candidate for developing a core set of COAs for use in regulatory review. If the FDA had a robust set of standard core measures of FO from which to evaluate the risks and benefits of multiple treatments, it would significantly advance its mission to promote patient-centered drug development. This represents an unmet need. Figure 1, adapted from Wilson and Cleary, places FO in the context of chronic disease treatment.[3] Moving from left to right across the figure, biological and physiological factors associated with many chronic diseases and disorders will produce symptoms. Often, treatments for those disorders cause side effects. Both symptoms and side effects can, in turn, adversely affect function. These symptoms and functional deficits affect more general perceptions we have about health and well-being, which in turn influence patients' HRQOL. This project focuses on the black box within Figure 1, namely symptoms, consistent with a recent FDA perspective on PRO labeling in oncology and provides a framework for building a context of use for a FO COA.[4]

Figure 1. Clinical outcome assessment (COA) model for chronic diseases and disorders



1.3 Context of Use

Incorporating feedback from the FDA and stakeholder groups, we propose that this COA set be used in the following nephrotic syndrome population:

1. Ages 2 years (24 months) and older; AND
2. Populations with Primary Nephrotic Syndrome Conditions: Focal segmental glomerulosclerosis (FSGS), Minimal Change Disease (MCD), IgM nephropathy, Membranous Nephropathy (MN), and childhood-onset nephrotic syndrome not specified.

We do not intend to exclude individuals who have received a kidney transplant at this time, and we will exclude dialysis dependent individuals. Analysis will include stratification of the native kidney disease and transplant kidney disease nephrotic populations.

2 OBJECTIVE AND APPROACH

The goal of the gap analysis was to identify development and validation work that will be required for the final approval of the proposed COAs for NS. To meet this objective, we have reviewed data from a variety of sources including:

- Existing PROs relevant to edema in order to understand any gaps in the data that were used in the development of these measures and to identify high-value items that may be incorporated or adapted into the final COA set
- Medical literature on symptoms and functional issues associated with FO to describe condition and anchor information including disease phenotype, natural history, and impact on patients
- Quantitative data from the CureGN and NEPTUNE studies to identify and describe disease phenotypes and natural history

- Extant qualitative data to determine if there are populations or concepts that may be insufficiently represented.

The overall approach for use of these sources was to first consider each, individually, drawing conclusions about potential gaps. Then, we aggregated gaps identified from the individual sources to draw overall conclusions and generate recommendations for next steps in development of our COA.

3 EXISTING PRO AND OBSRO MEASURE REVIEW

3.1 Objective and Methods

The objective of our review of known, relevant measures was to determine the potential for incorporating previously developed items into the final Prepare-NS COA set. Existing measures were reviewed against the context of use to identify contextual and conceptual coverage and gaps. The analysis identified where more data is needed to ensure complete coverage of evidence for the context of use. This approach aligns with FDA guidance on developing content-valid, disease-specific measures with demonstrated importance to the targeted patients and the context of use.

3.2 Results

3.2.1 Observer-reported outcome measures

We were unable to identify any ObsROs for use in the NS population.

3.2.2 Patient-reported outcome measures

We identified three PROs developed specifically for FSGS and MCD; two of the NS diagnoses that are being considered as a part of this review. All identified measures were developed by a subgroup of members of the Prepare-NS project team. In an effort to mitigate potential bias, members of the Prepare-NS team who were not involved in the development of these measures conducted this independent review. This review included: 1) the measures themselves (Appendixes 1-3); 2) related publications;[5,6] 3) technical summaries (Appendix 3); and 4) concept elicitation interview guides (Appendixes 3 and 4). Although the materials were reviewed in their entirety, this review of measures is limited to the evaluation of existing data as it related to the approved context of use for this project. More specifically, we have limited our focus to concepts related to edema and fluid overload as a result of NS.

FSGS Symptom Diary and the FSGS Symptom Impact Questionnaire. The FSGS Symptom Diary and the FSGS Symptom Impact Questionnaire are two PROs that are comprised of 43 items designed to support a comprehensive assessment of symptoms and symptom impact in adults with FSGS. The PROs were developed using qualitative research methods following FDA guidance to ensure that the measures are population-specific and that the concepts measured

are important to respondents. In the development of these PROs, participants engaged in concept elicitation and cognitive debriefing interviews to ensure item relevancy, comprehensiveness, and understandability. Clinical advisors were engaged to ensure the interview guides were consistent with clinical experience. The PROs were drafted based on concept elicitation findings, a literature review, and clinical advisor input; they include content coverage of patient-defined domains of disease such as fatigue, pain and edema. These PROs will be collectively referred to as the "FSGS PRO".

FSGS-MCD PRO. The FSGS-MCD PRO was developed to meet the need for a multidimensional disease-specific PRO for use in the pediatric population. It is adapted from the Adult FSGS PRO and includes additional data collected from children and adults with FSGS, as well as both children and adults with MCD. As in with the development of the FSGS Symptom Diary and the FSGS Symptom Impact Questionnaire for adults, and aligned with 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 disease-specific content (I.e., FSGG and MCD) and has undergone readability and translatability reviews.

3.2.2.1 Context of use coverage

Table 1 shows components of the overlap between the proposed context of use and their representation in the data used to create the FSGS PRO and the FSGS-MCD PRO measures.

Table 1. Overlapping Components of FSGS PRO and FSGS-MCD PRO

Proposed age group	Proposed disease	FSGS PRO	FSGS-MCD PRO
8-17 years	FSGS		X
	MCD		X
	Childhood-onset nephrotic syndrome not biopsied		X
18+ years	FSGS	X	X
	MCD		X

Age. All measures reviewed in this analysis use concept elicitation and cognitive debriefing data from adults ages 18 and older. Only the FSGS PRO set an upper age limit (65 years) for study inclusion. The average age of adult participants was 41.5 years (range 29-59 years). The FSGS-MCD PRO did not include an upper age limit; average participant age was 52.1 years (range: 8-72 years). However, only the FSGS-MCD PRO was developed using data from pediatric participants, with 11 participants ranging in age from 8-13 and 10 participants ranging in age from 14-17. Neither measure includes data from participants with ages 2-7 years.

Diagnosis. Diagnostic inclusion criteria in the FSGS PRO Development study were limited to idiopathic FSGS of a maximum of 60 months duration since diagnosis. Results from 30 concept elicitation and 9 cognitive interviews for patients with primary FSGS were used to develop the FSGS PRO. The FSGS-MCD PRO was developed using input from patients with FSGS and MCD and included a subset of patients with childhood-onset nephrotic syndrome not biopsied. MN and IgM nephropathy were not included in any age group in prior FSGS/MCD PRO measure development. Transplant recipients were excluded from both studies.

3.2.2.2 Concept coverage

Table 2 displays interview questions directly related to edema caused by nephrotic syndrome.

Table 2. Select Interview Questions from FSGS & FSGS – MCD PRO Development Studies

Measure	Interview question
FSGS PRO	Some people with FSGS experience edema or swelling. Have you **ever** experienced edema or swelling since being diagnosed? If yes, describe where you have/had swelling. *(Probe: face, feet, hands, stomach/abdomen, back, all over)* How, if at all, does/did swelling impact your ability to carry out your usual daily activities? *(Probes: perform household chores, work, school, exercise, socialize, wear the type of clothes you want to wear, eat, sleep)*
	How does/did the swelling make you feel? *(Probes: less comfortable around others, afraid of not being accepted because of your appearance?) Do you feel self-conscious when you have swelling? (Probe: Are there certain times you feel more/less self-conscious?) If they indicate abdominal swelling, ask the following:* Have/did you experience any specific issues such as muscle or abdominal cramping, pain, diarrhea, nausea, constipation, or bloating? If yes, please describe. Does the swelling you experienced in your stomach affect your diet or appetite? How?
FSGS-MCD PRO	Have you **ever** had swelling from your nephrotic syndrome or kidney problem/disease? Can you tell me more about that? Does swelling get in the way of your activities? *(Probes: housework/chores, work/school, hobbies, sports, spending time with friends/family, wearing the types of clothes you want to wear, eating, sleeping)*
	How does the swelling make you feel? *(Probes: less comfortable around others, afraid of not being accepted because of your appearance?) Do other people treat you differently when you have swelling?*

3.2.2.3 Interpretation and Proposed Approach

Age. Current data are available for patients ages 8 years and older but not for patients aged 7 years or younger across all conditions. We propose interviewing a sample of parent/guardians of affected children with nephrotic syndrome to meet this gap.

Diagnosis. There is a gap in representation for IgM and membranous nephropathy. We will enrich participant population by including transplant recipients who were excluded from previous studies. Concept elicitation and cognitive debriefing with patients with these conditions are proposed to fill this gap.

Edema. There is a gap in knowledge of specific parts of the body where swelling resulting in functional limitations. The FSGS-PRO interview guide included a prompt to ask about swelling locations on the body, but this was not evaluated in the FSGS-MCD PRO study. As a result, data are missing on swelling location for individuals of any age with MCD and for children with FSGS. We propose including a checklist assessment of body parts to be referenced during subsequent interviews.

Kidney Transplant Recipients. There is a gap in measures that address symptoms and impact of FO in kidney transplant recipients who have recurrence of nephrotic syndrome or have *de novo* occurrence of nephrotic syndrome after transplant receipt. We propose to include kidney transplant recipients as an additional population not formally included in our context of use.

Both interview guides include a question about the impact of edema on functional status, but a direct link between swelling and functional limitations was not made in the final measures. The presence of pain is also assessed through concept elicitation interviews, but a direct link between edema and the presence of fatigue, pain (i.e., pain caused by edema, and the characteristics of this pain), decreased mobility, for example, are not represented on the final measures. Recognizing the challenges of differentiating sources of impacts (e.g., swelling related pain or other diseases related pain), we will invite participants to provide indicate which areas of the body are causing functional limitations due to edema.

4 LITERATURE REVIEW

4.1 Objective

The objectives of this scoping review were (1) to define the scope of signs and symptoms associated with primary proteinuric kidney disease, NS, and FO and (2) to identify items, tools or measures available to assess FO signs, symptoms and/or impact in NS, primary proteinuric kidney disease, or other health conditions. The results of this scoping review will inform our overall gap analysis leading to recommendations for COA development.

4.2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) offers an extension for scoping reviews (PRISMA-ScR).[7] We developed a formal protocol, which was submitted to the FDA on 07/16/2021 for review and approved on 07/30/2021.

4.2.1 Selection Criteria and Search Strategy

Type of intervention: All

Population of studies: Both children and adults

Publication Date: 1990-present

Location: No geographical limits

Table 3. Scoring Interview Eligibility Criteria Table

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—Sample from PubMed database

#	Search Strategy
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 accumulat*"[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]
23	"shortness of breath"[tw] OR dyspnea[tw] OR "Dyspnea"[Mesh]

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

24	"exercise intolerance"[tw] OR "exercise tolerance"[tw] OR "exercise capacity"[tw] OR fatigu*[tw] OR "Exercise Tolerance"[Mesh] OR "Fatigue"[Mesh]
25	Discomfort[tw] OR pain[tw] OR "Pain"[Mesh]
26	Mobil*[tw] OR immobil*[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])

Data Sources and Searches. The project information specialist (EC) conducted electronic searches of PubMed, Embase, Cochrane Central, Scopus, and Google Scholar from 1/1/1990 to 09/01/2021 using the selection criteria and search strategy above. These results appear in the left arm of the PRISMA diagram. During study selection and data extraction, we observed that this strategy did not capture some trials in nephrotic syndrome known to our group to include potentially relevant HRQOL measures and speculated “edema” or “overload” not appearing in the published manuscript as plausible explanation. To capture these trials, we repeated the earlier search without “edema”/”overload” and filtered for clinical trials. Studies published in the interval since the first search (09/01/2021 - 02/17/2022) also were captured. These results appear in the right arm of the PRISMA diagram.

Study Selection. Randomized clinical trials (RCTs), nonrandomized and single-arm clinical trials, and cohort studies were eligible for inclusion. Case studies were excluded, as were studies with only conference abstracts and/or posters, studies not published in English, and studies involving animals only. We used the evidence synthesis tool DistillerSR to screen and filter titles and abstracts for potential relevance. Studies were screened by two independent reviewers (ES and RS). All abstracts identified for potential inclusion by both reviewers were marked for full-text review. Full-text articles for all candidate abstracts identified for inclusion by each reviewer then underwent dual independent review. Disagreements were resolved through discussion.

Data Extraction. Data were extracted by reviewers (ES and RS) using a standardized Excel spreadsheet (Microsoft Corp). Variables extracted into the spreadsheet included first author, year of publication, study design, sample size/characteristics, and high-level findings. The spreadsheet was independently verified by the second reviewer (ES and RS), and disagreements were resolved through discussion.

Data Synthesis. Synthesis of evidence was qualitative and consisted of describing study design/population and study use of PRO/ORO. Although we did not conduct a formal assessment of study quality, our synthesis recognized some studies were more rigorous than others.

4.3 Results

Literature selection

Our initial search strategy yielded 1,337 unique records (Figure 2). After title and abstract screening, 174 abstracts were identified for full-text review. A total of nine studies met eligibility criteria. Characteristics of included studies are provided in Table 4. An additional seven articles were captured in the supplemental search of clinical trials.

Signs and Symptoms

Table 4 captures the range of symptoms associated with NS (with reported frequency when available).

Measures

Measures inclusive of edema/fluid overload content. Edema often was reported as binary (yes/no, any/none, etc.),[8] and the presence of edema was correlated with lower scores on general HRQOL of measures. [9-12] One study reported edema in more detail based on location/amount and correlated edema severity with general HRQOL measures.[13] One general HRQOL measure, the PedsQL, has a module including the item "I get swelling in my face". Importantly, this module is geared toward end stage renal disease (ESRD), so while the item can be used in patients with nephrotic syndrome, it was developed for a different population.

Measures without edema/fluid overload content. Established, non-specific HRQOL measures used most frequently were Patient-Reported Outcomes Measurement Information System (PROMIS)[14] and Pediatric Quality of Life Inventory (PedsQL).[15]

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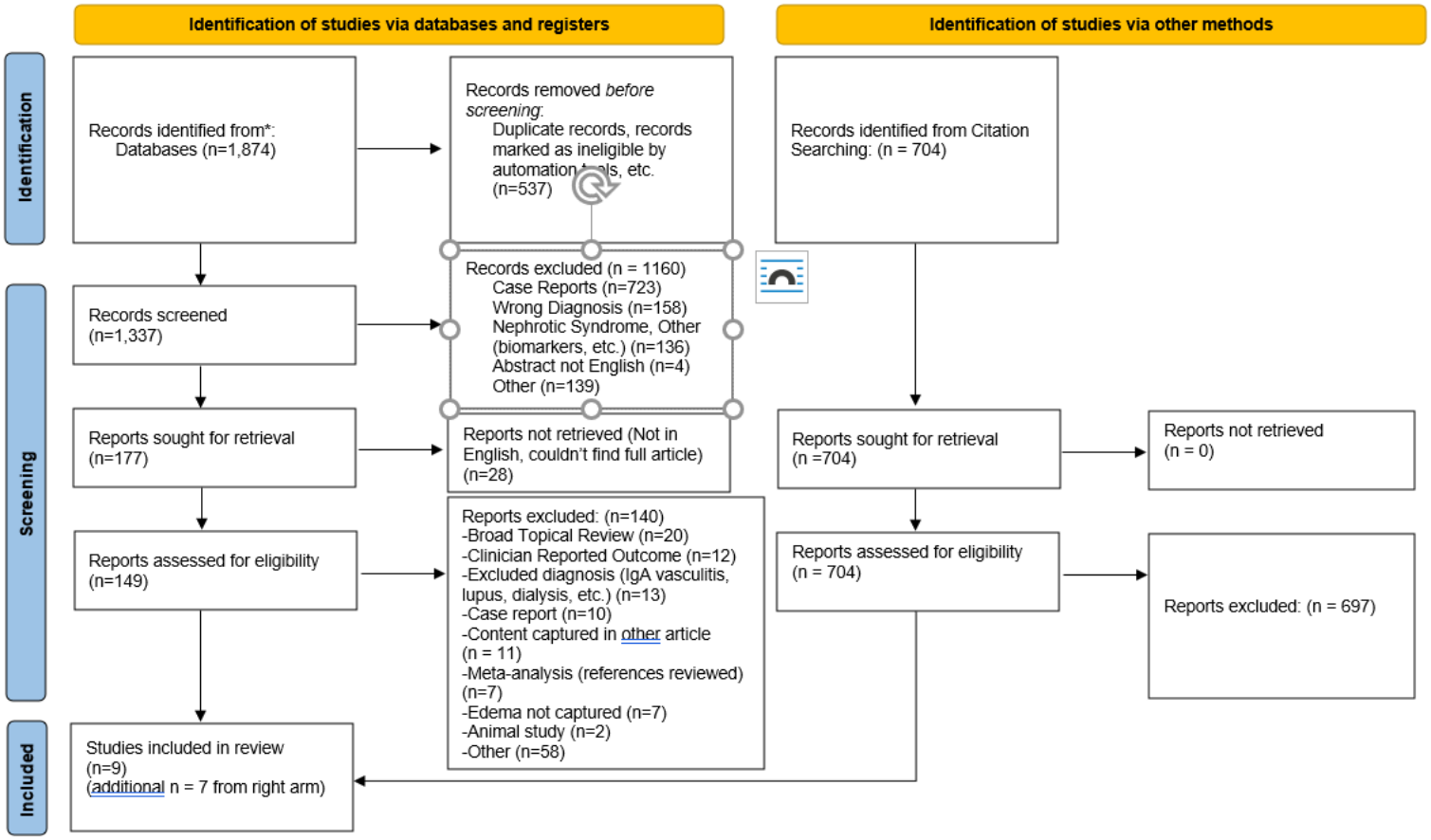
Table 4. Studies and Measures Included in Scoping Review

Title	Author	Year	Study Design	Diagnosis	Age/ Population	Measure(s) Used
Efficacy and safety of Sparsentan compared with Irbesartan in patients With primary focal segmental glomerulosclerosis: Randomized, controlled trial design (DUET)	Komers R	2017	Randomized controlled trial	Primary FSGS		PedsQL, SF36
Rituximab or Cyclosporine in the treatment of membranous nephropathy	Fervenza FC	2019	Randomized controlled trial	Membranous nephropathy	130 adults	KDQOL SF
Prevention of relapses with levamisole as adjuvant therapy in children with a first episode of idiopathic nephrotic syndrome: study protocol for a double blind, randomised placebo-controlled trial (the LEARNS study)	Veltkamp F	2019	Randomized controlled trial	Idiopathic nephrotic syndrome	92 children (age 2-16)	PedsQL, SDQ
Quality of life in children with severe forms of idiopathic nephrotic syndrome in stable remission: A cross-sectional study	Roussel A	2019	Observational	Idiopathic nephrotic syndrome	110 children (age 7-17)	KINDL
Study design of the Phase 3 Sparsentan versus Irbesartan (DUPLEX) study in patients with focal segmental glomerulosclerosis	Komers R	2020	Randomized controlled trial	FSGS	300 adults and children (age 8-75)	KDQOL (adults only); PedsQL (peds only); EQ-5D (adults and peds)
Peptide GAM immunoadsorption in anti-PLA2R positive autoimmune membranous nephropathy: The PRISM trial	Hamilton P	2022	Single arm prospective	Membranous nephropathy	12 adults	EuroQOL
Daily low-dose prednisolone to prevent relapse of steroid-sensitive nephrotic syndrome in children with an upper respiratory tract infection: PREDNOS2 trial	Christian MT	2022	Randomized controlled Trial	Relapsing steroid sensitive nephrotic syndrome	365 children (mean age 7.6±3.5 years)	Achenbach Child, Behaviour Checklist, PedsQL

4.1 Discussion

The available data suggest fatigue and changes in appetite are especially prevalent among patients with NS; pain and impaired activities of daily living are reported more variably. A targeted PRO could help make relevant distinctions, such as discomfort secondary to swelling versus other pain. There is a paucity of PRO and absence of ObsRO of FO for use in the NS population. Despite the well-known negative impact of FO to patients' daily living, few studies have examined the impact of FO on NS patients using developed and validated PRO or ObsRO measures.

Figure 2. PRISMA Flow Diagram



5 QUANTITATIVE ANALYSIS OF CUREGN AND NEPTUNE DATA

5.1 Objective

The goal of this analysis was to use extant quantitative PRO data from the CureGN and NEPTUNE databases to identify which additional symptoms were most associated with fluid overload. These analyses were designed to help determine impacts of fluid overload that could be measured in the COA. To do so, we compared level of symptom burden and HRQOL between patients with and without documented edema. The analysis was stratified by adult and child.

5.2 Methods

5.2.1 Datasets

The analyses were performed in parallel on the CureGN and NEPTUNE datasets. Details of each are given below.

CureGN. The Cure Glomerulonephropathy Network (CureGN; NIDDK, UM1DK100845) project has over 2,400 participants with FSGS, MCD, MN, and IgA nephropathy.[16] The CureGN cohort includes both pediatric and adult NS patients who are recruited from sites throughout the United States, Canada, and Europe. Participants are followed longitudinally to better understand the causes, therapies, and disease progression of kidney disease. CureGN collects epidemiological, biomarker, genetic, and PRO data, including symptom assessments and HRQOL measures, and biospecimens annually. There is rolling enrollment, and most data, including PROs, are collected every four months. The CureGN infrastructure will be leveraged to recruit patients, clinicians and caregivers for semi-structured interviews in the qualitative study and for the visits, data and biospecimen collection procedures will be leveraged for the quantitative study.

NEPTUNE. The Nephrotic Syndrome Study Network (NEPTUNE; 2U54DK083912-11) is an NIH-sponsored rare disease clinical research network that includes a 24-site (USA and Canada) prospective observational cohort of over 700 children and adults with incident FSGS, MCD, MN, childhood onset-NS, and other conditions.[17] The overarching objective of the NEPTUNE program is to provide a research infrastructure, including a patient cohort, demographic and clinical phenotyping data, biospecimens, central laboratory and pathology cores and collaborators, to support a wide spectrum of clinical and translational research. NEPTUNE uses REDCap to collect patient reported data, including HRQOL and SMS to collect frequent targeted data collection by text messaging, to enrich the data collected via standard in-person and virtual study visits. Visits are conducted every 4 months in year 1 and every 6 months thereafter and include the collection of data and biospecimens and a limited physical exam.

5.2.2 Inclusion and Exclusion Criteria

Two separate populations are defined for these gap quantitative analyses: adults (≥ 18 years at time of PRO data collection) and children (< 18 years old at time of PRO data collection). In addition, for both CureGN and NEPTUNE, the following inclusion criteria for adults were applied when drawing records for each for analysis:

- Joined CureGN study by 12/6/2021 or joined NEPTUNE by 09/22/2021,
- Aged ≥ 2 years old at time of study enrollment,
- Diagnosis of a primary NS condition, and
- At least one assessment of edema (patient or clinician reported) documented.

In addition, we applied the following exclusion criterion:

- Developed end-stage kidney disease before first reported edema.

After these criteria were applied, we determined the number of patients available for analysis among the adult and child cohorts separately.

5.2.3 Measures

In both the CureGN and NEPTUNE datasets, adult measures from the Patient Reported Outcomes Measurement Information System (PROMIS®) domains were administered: Global Health (generated Global Physical and Global Mental Health summaries), Physical Function, Fatigue, Pain Interference, Sleep Disturbance, Anxiety, and Satisfaction with Participation in Social Roles and Activities. For the child cohorts, measures for the following PROMIS domains were administered: Mobility, Fatigue, Sleep Disturbance, Pain Interference, Anxiety, Depression, Stress, Peer Relationships, and Global Health. For each, a T score with referenced group mean of 50 and standard deviation of 10 is generated. We rescored measures where higher scores indicate worse health (e.g., fatigue, anxiety) so that higher scores indicated better health for all PROMIS measures. For PROMIS scales, differences as a small as one-third to one-half of a standard deviation (3-5 points) can be considered clinically meaningful.[18,19] Therefore, we considered differences of ≥3 points as indicators of clinically-relevant symptoms or quality of life domains for consideration in future COA development.

In addition to PROMIS measures, for the child cohort, the PedsQL 8-12 and PedsQL13-18 instruments were administered. From these instruments, the Physical, Emotional, Social, School, and Psychosocial scale (a combination of the Emotional, Social, and School scales) scores were calculated. All PedsQL scales are linearly transformed to a 0-100 scale and negatively worded questions are reverse scored so that higher scores indicated better health. The following guidelines were used to identify score differences large enough to be considered clinically important on PedsQL: Physical Health = 7 points; Emotion: 9 points; Social Functioning = 9 points; School Functioning = 10 points; Psychosocial Total = 6 points; Instrument Total = 5 points.[15]

At the time of their PRO assessment at or after their first episode of edema, patients were coded as having an episode of edema by physician conducted physical exam or self-report. This allowed the

cross-sectional assessment of the influence of edema on HRQOL and symptom burden. Demographic and baseline disease characteristics were also captured.

5.2.4 Statistical Analyses

We summarized patient characteristics (demographics and baseline disease characteristics) with frequencies and proportions or medians and interquartile ranges (IQR), stratified by age group (adult and child). We estimated mean differences in symptom burden and HRQOL between patients with and without edema, stratified by age group. 95% confidence intervals (CI) were calculated for the mean differences. A 95% CI crossing 0 indicated that the difference was not statistically significant at $p<0.05$. In addition, we examined whether the point estimate exceeded thresholds for important differences.

5.3 Results

After applying the inclusion and exclusion criteria and pooling the CureGN and NEPTUNE datasets, records from 1246 adults and 432 children were available for analysis of PROMIS measures and 38 children were available for analysis of PedsQL data. (Appendix E) The vast majority of both adults (92%) and children (75%) had reported edema. The median time from study entry to the quality of life assessment used for this analysis was 0 months for adults and 2 months for children. The median age of the adult sample was 48 years, while this value for the child sample was 11 years. The largest proportions of both adults (67%) and children (53%) were White/Caucasian race, followed by Black/African Americans (adult = 20%, child = 29%). Hispanic/Latino ethnicity was self-reported (adult = 13%, child = 16%). The most common diagnosis for adults was membranous nephropathy (42%), and minimal change disease for children (53%). (Table 5.)

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Table 5. Characteristics of CureGN and NEPTUNE Participants with PROMIS Measures

	Adult (N=1246)	Child (N=432)
Edema at PROMIS assessment, n (%)		
No	101 (8%)	101 (23%)
Yes	1142 (92%)	325 (75%)
Unknown/missing	3 (0)	6 (1)
Age at PROMIS assessment, median (IQR)	48 (32, 60)	11 (8, 14)
Time from entry to PROMIS assessment (months), median (IQR)	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%)
Multi-Racial	22 (2%)	27 (6%)
Unknown/missing	42 (3%)	19 (4%)
Ethnicity, n (%)		
Hispanic or Latino	160 (13%)	69 (16%)
Not Hispanic or Latino	1074 (86%)	354 (82%)
Unknown/missing	12 (1%)	9 (2%)
Diagnosis, n (%)		
Minimal Change Disease	272 (22%)	228 (53%)
FSGS	451 (36%)	140 (32%)
Membranous Nephropathy	521 (42%)	30 (7%)
Childhood onset nephrotic syndrome not biopsied	2 (0%)	34 (8%)

Comparisons of the HRQOL domains between patients with and without edema are shown in the forest plots in Figure 3 Panels A, B, and C. The sample size for each measure varies because of missed

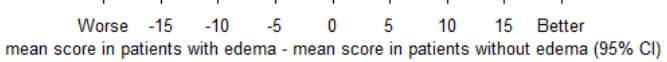
PRO assessments. For each, the mean difference reflects the mean score for patients with edema vs. those without edema. Since all scores have been calculated so that higher scores indicate better health, a negative difference indicates worse symptoms or HRQOL for patients with edema. Among adults, the largest mean negative differences were observed for Fatigue (-6.73 points; 95% CI: -8.71, -4.75), Global Physical Health (-6.34 points, 95% CI: -8.34, -4.33), Anxiety (-5.79 points; 95% CI: -7.52, -4.07) and Physical Function (-5.71 points; 95% CI: -8.41, -3.01). 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% confidence intervals 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 (-7.76; 95% CI: -15.82, 0.31), Fatigue (-7.03; 95% CI: -9.76, -4.30), Depression (-5.28; 95% CI: -8.35, -2.20), Anxiety (-4.90; 95% CI: -6.64, -3.16), Global Health (-3.54; 95% CI: -5.72, -1.36) and Mobility (-3.0; 95% CI: -5.86, -1.73) (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. The upper bound for the 95% CI of the estimate for Pain Interference was 0.31, slightly surpassing 0 – thus near the nominal p=0.05 level. For the PedsQL instruments, only the Physical domain surpassed the threshold for clinically meaningful difference (-12.96 points; -19.49, -6.42) (Panel C).

Figure 3. Comparison of Symptom and HRQOL Domains

Panel A. Adult PROMIS Measures

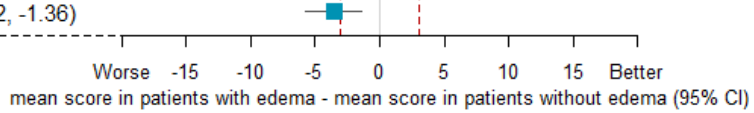
Domain	Measure	N Edema	N Without Edema	Mean Diff (95% CI)
Physical	Global Assessment Physical Health T-score	1024	88	-6.34(-8.34, -4.33)
	Physical Function T-score	163	57	-5.71(-8.41, -3.01)
	Fatigue* T-score	1130	96	-6.73(-8.71, -4.75)
	Pain* Interference T-Score	111	7**	-7.57(-15.62, 0.47)
	Sleep* T-score	1060	77	-2.35(-4.33, -0.37)
Mental	Global Assessment Mental Health T-score	1024	89	-2.8(-4.73, -0.88)
	Anxiety* T-score	1121	95	-5.79(-7.52, -4.07)
Social	Satisfaction with Participation in Social Roles T-Score	111	7**	-6.32(-15.66, 3.02)

** PROMIS domains were transformed so that higher scores indicate better HRQOL.*
*** The small sample size is caused by PROMIS domains only existed in 1st phase of NEPTUNE study.*



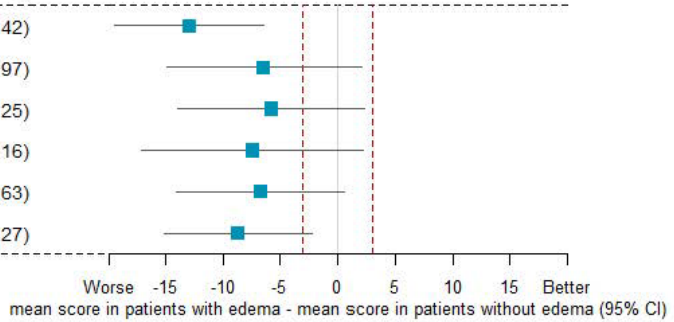
Panel B. Child PROMIS Measures

Domain	Measure	N Edema	N Without Edema	Mean Diff (95% CI)
Physical	Mobility	313	97	-3.8(-5.86, -1.73)
	Fatigue	314	96	-7.03(-9.76, -4.3)
	Pain	21	5	-7.76(-15.82, 0.31)
Mental	Anxiety	314	94	-4.9(-6.64, -3.16)
	Depression	67	55	-5.28(-8.35, -2.2)
	Stress	25	35	-3.37(-7.98, 1.24)
Social	Peer Relationships	21	5	-0.07(-10.22, 10.08)
Global	Global	296	89	-3.54(-5.72, -1.36)



Panel C. PedsQL Measures

Domain	Measure	N Edema	N Without Edema	Mean Diff (95% CI)
Physical	Physical	38	67	-12.96(-19.49, -6.42)
Mental	Emotion	38	67	-6.49(-14.95, 1.97)
Social	Social	38	66	-5.84(-13.93, 2.25)
	School	38	65	-7.48(-17.12, 2.16)
Psychosocial	Psychosocial	38	67	-6.72(-14.07, 0.63)
Total	Total	38	67	-8.74(-15.2, -2.27)



5.4 Discussion

Across age groups, we observed that edema was associated with experience of multiple physical symptoms. These included physical functioning and fatigue. In addition, though samples of patients with pain scores were too small to interpret with confidence, the point estimates for pain associated with edema were very large. Though less useful to COA development in the context of drug development, global and overall physical health detriment was also associated with edema and helps provide context for our findings around physical symptoms and their ultimate impact on patients' lives.

6 QUALITATIVE ANALYSIS OF EDEMA-RELATED SYMPTOMS IN NS

6.1 Summary of review of published qualitative data

6.1.1 Objective

The goal of this analysis was to use published qualitative data to identify the gaps that will inform the remainder of work required to complete PRO and ObsRO measure development.

6.1.2 Results

Our published qualitative data informing the development of the FSGS-MCD PRO identified several key physical symptoms and HRQOL domains, including (percentages indicate the combined sample of children and adults with FSGS and MCD, N=48): 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 (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.[20] Published concept elicitation data informing the development of the FSGS Impact Questionnaire and Symptom Diary describe patient-reported swelling in 100% of participants (N=25).[6] The most common locations of swelling were from the waist down, including legs, knees, feet, and ankles (80%); of the stomach/abdomen (52%); of the face, eyes, or skull (40%); of the fingers, arms, or hands (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 (n=3). The impacts of these symptoms were also described. 52% of participants reported FSGS affects 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.

6.1.3 Discussion

The findings from these studies suggest that the commonalties between HRQOL in FSGS and MCD, as well as the commonalities in HRQOL between adults and children, should allow for the development of an HRQOL patient-reported outcome measure that can be used in children (ages 8 and above) and adults, as well as across the proposed disorders, and is appropriate for use supporting FDA-based labeling claims.[21,22] The most important or common symptoms or HRQOL domains identified were related to physical health, tended to be oriented toward the lower extremities where swelling in those locations was concerned. These data suggest significant impacts of swelling on physical function, pain, sleep, dyspnea, and appetite.

6.2 Focused secondary analysis of existing transcripts

6.2.1 Objective

The goal of this analysis was to use unpublished qualitative data to identify the gaps that will inform the remainder of work required to complete PRO and ObsRO measure development. Specifically, we aimed to describe lifetime experience of swelling as well as the frequency of swelling for different body parts among children and adults with FSGS and MCD.

6.2.2 Methods

This secondary analysis of qualitative data examined both lifetime experience of edema for both children and adults with FSGS, as well as children and adults with MCD. In addition, we reviewed 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. 48 children and adults with FSGS and MCD were enrolled in this study at three sites: 1) the University of Michigan, 2) New York University-Langone Health and 3) Levine Children's Hospital/Atrium Health. Each participant had a confirmed diagnosis of FSGS or MCD. Other inclusion criteria were 1) an eGFR > 30 ml/min/1.73 m2; 2) proteinuria in the past 12 months; 3) ability to provide informed consent or assent; and 4) were conversant in English. We excluded patients with ESKD and history of renal replacement therapy, <8 years of age, or had a co-existing chronic or severe acute health condition. All participating sites obtained IRB approval prior to starting the study. Semi-structured interviews were conducted with participants. Open-ended questions asked participants to express what the term "Health Related Quality of Life" meant to them, as well as what they believed to be the most important aspects of HRQOL to them. Prompts were provided across multiple domains of HRQOL to keep the conversations focused.

6.2.3 Results

The frequency of patients endorsing swelling for a specific body part is summarized in Table 6 Over 90% of total participants reported some swelling. The most common areas where swelling was articulated in the interviews were the abdomen/stomach, lower leg (shin and knee), ankles, feet/toes, and the upper leg/thigh; over half the sample mentioned experiencing swelling in these areas. Least

frequently endorsed areas of swelling were in the genitals and buttocks. Patients with FSGS were most likely to describe ankle swelling, while patients with MCD most frequently endorsed abdomen or stomach swelling. The biggest difference between FSGS patients and MCD patients was with respect to endorsed swelling in the abdomen (33% of FSGS patients vs. 85% of MCD patients), the upper leg/thigh (29% of FSGS patients vs. 82% of MCD patients), and the lower leg (33% of FSGS patients vs. 82% of MCD patients).

Table 6. Percentages of Patients Reporting Swelling by Body Part

Body Part	FSGS			MCD			Combined FSGS and MCD Sample
	Children (n=11)	Adults (n=10)	Combined (n=21)	Children (n=11)	Adults (n=16)	Combined (n=27)	N = 48
Abdomen or Stomach	36.4	30	33.3	72.7	93.75	85.2	62.5
Ankles	36.4	70	52.4	45.5	75	63.0	58.3
Arms	18.2	10	14.3	27.3	37.5	33.3	25
Back	0	0	0	18.2	18.75	18.5	10.4
Buttocks	0	10	4.8	0	6.25	3.7	4.2
Eyes	45.5	0	23.8	45.5	43.75	44.4	35.4
Face	36.4	10	23.8	45.5	50	48.1	37.5
Feet or Toes	36.4	60	47.6	63.6	68.75	66.7	58.3
Genitals	0	10	4.8	0	12.5	7.4	6.25
Hands or Fingers	18.2	0	9.5	18.2	31.25	25.9	18.75
Lower Leg (shin and knee)	27.3	40	33.3	72.7	87.5	81.5	60.4
Neck	0	0	0	0	0	0	0
Overall Body or Nonspecific	90.9	70	81.0	100	100	100	91.7
Skin	36.4	40	38.1	27.3	43.75	37.0	37.5
Upper Leg or Thigh	27.3	30	28.6	72.7	87.5	81.5	58.3

Data are presented as percentage of patients endorsing swelling for a specific body part.

6.2.4 Discussion

This analysis identified body parts where swelling is most common, which tended to center around the trunk and lower extremity. However, we note that swelling occurred in many various body parts with less frequency, but this still may be meaningful to patients. We also note that there was a greater presence of non-specific swelling among FSGS patients vs. MCD patients, though within diagnoses, results were fairly consistent across age groups. These results will be instructive in the COA construction in that they corroborate other results pointing to lower extremity as an area of the body that may be especially impacted by FO. We also will feel more confident in aligning the content of the PRO and ObsRO instruments, since few inconsistencies between age groups were observed.

7 SUMMARY OF IDENTIFIED GAPS AND RECOMMENDATIONS FOR COA CORE SET

Our extant PRO review, scoping literature review, analysis of quantitative data, and analysis of qualitative data helped us identify key gaps to address when developing our FO-focused COA development. There were some consistent messages across the sources, but each source also contributed unique, relevant information. The major gaps we identified along with key recommendations for our COA core set development are given in Table 7.

Table 7. Gaps Identified and Recommendations for Next Steps

Gap	Recommendation for COA Development
No measures for patients aged <8 years	Develop an ObsRO
Concept elicitation on FO and impact of FO to demonstrate the impact of fluid overload on symptoms and HRQOL with adults and children with MCD, FSGS, childhood onset NS. Concept elicitation is fully absent from adults and children with IgM nephropathy, membranous nephropathy, and nephrotic syndrome recurrence in kidney transplant recipients.	Conduct a new set of concept elicitation interviews to include missing diagnoses and age groups
Current PROs were not developed specific for FO and FO specific concerns might be not fully-captured by these generic items. Some symptoms (e.g., appetite changes) were not included in the current PROs used on FO.	Identify potential items covering FO associated impact on concepts identified as bothersome in concept elicitation, e.g., physical function, fatigue, pain, sleep disturbance, appetite changes, and dyspnea

The recommendations described in Table 7 provide guidance for next steps in our activities in the UG3 phase of our project. By acting on these recommendations, while drawing on the available PRO measures, both specific to FO and covering related symptoms, we are confident in our ability to develop the core COA set by the end of the UG3, which would then be psychometrically evaluated in the UH3 phase.

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