The Canadian Childhood Nephrotic Syndrome Project (CHILDNEPH)

NCT – Pending

February 25, 2015

1.0 OVERVIEW

Nephrotic syndrome is the most common acquired kidney disease in children.[1] Affected children have recurrent episodes (or relapses) of proteinuria that may lead to life-threatening complications including sepsis, peritonitis and thromboembolism.[2] The goals of treatment are to induce remission of proteinuria, reduce the number of relapses, minimize toxicity of treatments and delay kidney damage.[3] The first-line treatment for nephrotic syndrome is oral steroids, and many children will need repeated courses of steroids for relapsing disease.[2,4] However, steroid treatment is associated with many side effects, including obesity, growth retardation, hypertension, cataracts, poor bone health, and cosmetic effects.[2,5-15] Various other non-steroid immunosuppressive drugs are often used in the course of illness to decrease frequency of relapses and to avoid side effects of prolonged and recurrent steroid use.[16] Treatment protocols for relapsing nephrotic syndrome are therefore complex, requiring multiple drugs and multiple courses of therapy over long periods of time for disease control.

International clinical practice guidelines are available to guide treatment of nephrotic syndrome;[17] however, many of the recommendations are based on poor quality evidence and very few randomized controlled trials - leading to considerable debate among physicians regarding best treatment approaches.[18,19] As a result, drug treatment protocols and processes of care for childhood nephrotic syndrome are highly variable among physicians and care centres; evidence practice gaps also exist.[20,21] In a survey of Canadian pediatric nephrologists, we found striking variation in dose and duration of steroids and second line agents reportedly used for first presentation and relapses of nephrotic syndrome.[22] Lack of consensus between physicians and centres regarding best treatment approach can lead to a frustrating experience for patients and families, poor satisfaction with clinical care, and sub-optimal outcomes.[19,23] Using a priority setting survey, we identified that addressing these issues in the management of childhood nephrotic syndrome is the top priority for the Canadian pediatric nephrology community.

In Canada, little research has been done to evaluate and improve outcomes of children with nephrotic syndrome. It is not known whether variability in treatments affects patient outcomes – addressing this problem is a necessary first step towards improving care and patient experience. A carefully constructed prospective longitudinal cohort with a large and generalizable sample of patients can help us answer this question. Therefore, we have established the first national prospective cohort of children with nephrotic syndrome with the overall goal to provide ***best care based on best evidence***.

Over the last 2 years, we received start-up funds from Canadian Institutes of Health Research (CIHR) and other sources to establish this cohort in 13 sites across Canada. We have enrolled 77 patients to date and have provided our preliminary data in this application. The funds received to date are inadequate to reach the sample size needed and to complete the observation period required to address the research questions as proposed *within this* application. We have noted in the proposal and budget, the progress of our ongoing work and where new funds are needed. We have also carefully considered past review committee comments in this re-submission.

We will use the prospective cohort to address the following 2 objectives:

Objective 1

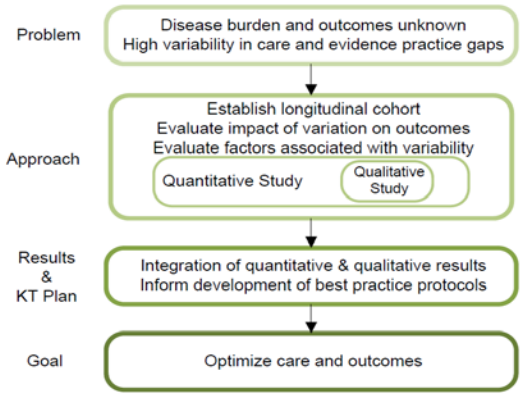
a) To determine the association of steroid dose prescribed (total dose prescribed during observation period divided by total number of days on treatment) and relapse rates (primary outcome defined as total number of relapses divided by total observation time).

Objective 2

a) to determine the associations between centre-, physician-, patient-level characteristics and i) steroid dose prescribed, and ii) length of steroid treatment for first presentation and subsequent relapses of nephrotic syndrome;

b) To identify reasons for practice variation in treatments for nephrotic syndrome between and among pediatric nephrology care providers and centres.

For Objective 1, we will evaluate association of steroid dose prescribed with relapse rates, adjusting for patient characteristics. For objective 2, we will use multi-level modeling with patients nested within physicians and physicians nested within health centres, to evaluate the association of patient-, physician- and centre-related factors with variability in steroid treatment dose prescribed. An embedded qualitative study utilizing focus groups of health care providers will enrich the quantitative results by providing an understanding of attitudes, beliefs and local factors driving variation in care at participating centres, while considering provider characteristics (training background, experience) and centre characteristics (use of standardized protocols). Quantitative and qualitative results will be integrated (using a convergent parallel mixed methods design) for interpretation at the end of study, and collectively inform strategies for development and implementation of best practice treatment protocols across centres to improve overall provision of care in this patient population. *See adjacent figure for overview of study.*



2.0 DISEASE BURDEN AND MANAGEMENT ISSUES

2.1 Childhood nephrotic syndrome is characterized by severe proteinuria, hypoalbuminemia and edema.[1] The incidence rate of nephrotic syndrome is 2 to 7 cases per 100,000 children per year and prevalence is estimated as 16 per 100,000 children.[1,24-26] In Canada, approximately 150 children will be diagnosed with nephrotic syndrome each year and there are an estimated 1,000 prevalent patients (data collected from participating sites, see attached support letters). Although the cause of this disease is unknown in most children, nephrotic syndrome can occur in association with genetic mutations in the components of the glomerular filtration barrier, comorbid conditions or environmental triggers.[1] Without treatment, children with nephrotic syndrome develop edema-related complications, pleural effusions, severe infections (e.g. peritonitis, pneumonia, sepsis), thromboembolism and eventually, progress to kidney failure or death.[27-29] Most (70-90%) children with nephrotic syndrome will have a relapsing course of proteinuria (range of 1 to >20 relapses during childhood) leading to significant morbidity.[10,30] Therefore, nephrotic syndrome is associated with substantial health system costs which include specialist and multi-disciplinary health care team visits, hospital admissions for control of edema, infection or thrombosis and for kidney biopsies.[31]

2.2 Steroids are the treatment of choice for first presentation and subsequent relapses of nephrotic syndrome. Clinical response to steroids is the most important predictor of disease course.[2] Steroid sensitive patients typically respond to treatment with remission of proteinuria within 2 weeks of therapy and maintain normal kidney function. Steroid resistant patients, defined as those who fail to achieve complete remission of proteinuria after 8 weeks of steroid therapy, have a high risk (>50% in 5 years) of kidney failure.[32,33] Approximately 90% of children with nephrotic syndrome are steroid sensitive, and they will be the focus of our study.[34,35] Among these patients remission is achievable with steroid treatment; however, relapses are common requiring multiple courses of steroids and steroid sparing immunosuppressive drugs - leading to significant side effects drug toxicity. Of the children who relapse, up to 50% will have frequent relapses (≥2 relapses within 6 months of first response or ≥4 relapses in any 12 month period) or become steroid dependent (2 consecutive relapses during tapering of steroid therapy, or relapse within 14 days of steroid cessation).[10,30] Steroid toxicity reported in children with nephrotic syndrome includes growth retardation and obesity,[7,9,13,36] hypertension,[11,37] posterior sub-

capsular cataracts,[6,12] decreased bone mineral density,[14,15] and impaired glucose tolerance.[8] Minimizing relapse rates and steroid exposure are the most important goals in caring for these patients and remain the most relevant clinical outcomes.

2.3 Steroid treatment protocols used for nephrotic syndrome today were developed over 40 years ago, and revised over time. These protocols were drafted as part of an international cohort study of children with nephrotic syndrome (International Study of Kidney Disease in Children, ISKDC) between 1967-1974, with the aim to induce remission of proteinuria and reduce risk of relapses.[34] Later in the 1980s and 1990s, clinical trial evidence generated by the German working group for pediatric nephrology supported that longer initial courses of steroid therapy led to fewer relapses over time.[38,39] As a result, many Canadian pediatric nephrology physicians and centres changed their steroid protocols from the original ISKDC regimen of 4 weeks of daily steroid therapy followed by 4 weeks of alternate day therapy to 6 weeks of daily steroid therapy followed by 6 weeks of alternate day therapy for first presentation of nephrotic syndrome (total therapy time increased to 3 months from 2 months). More recently, the results of a meta-analysis published in 2007 suggested prolonging therapy up to 6 months for first presentation of nephrotic syndrome may decrease the number of relapses over time compared to 3 month regimens[40] - prompting some physicians to adopt 6 month steroid protocols.

2.4 Although a reasonable body of evidence is available to guide practice, practice variation is common in nephrotic syndrome. The available evidence base for treatment of first presentation and relapses of nephrotic syndrome were synthesized and published in several systematic reviews, local guidelines,[2,40,41] and also in a recent international clinical practice guideline.[42] Nevertheless, lack of consensus regarding best treatment approaches is a well-known international phenomenon. Variation in care was documented in surveys of American pediatric nephrologists in 2000 and 2009; however, little has been done to address this problem in the United States or elsewhere.[20,21] We performed a similar survey which was sent to all Canadian pediatric nephrologists (n=58) and achieved a 69% response rate. The results showed significant variation in steroid protocols and also in the choice of steroid sparing drugs and biopsy practices (see manuscript attached, Samuel S, Pediatr Nephrol 2013). The total duration of steroid therapy ranged from a minimum of 7.5 weeks to a maximum of 26 weeks (median 16 weeks) for first presentation of nephrotic syndrome – likely contributing to considerable variation in cumulative steroid exposure among patients who may otherwise have similar clinical presentations. Sample protocols used by Canadian physicians and centres are shown in Appendix Tables 1a and 1b. The overall impact of this variability in steroid exposure on relapse rates of Canadian children with nephrotic syndrome has not been formally assessed and remains the most important and compelling unanswered question.

2.5 Patient-, physician- or centre-related factors may be associated with practice variation in nephrotic syndrome. Physicians make decisions about dose and duration of therapy while considering both efficacy and toxicity of drugs in the context of individual patient clinical presentations and preferences. Physicians may also be influenced by their training background, familiarity with the literature, and their work environments. In our survey of practice patterns, duration of steroid therapy prescribed was associated with year of graduation for physicians (i.e. years in practice) and the presence or absence of a standardized protocol in centres[43] – providing preliminary evidence that physician and centre-specific factors also play a role in variation of care. We also found widespread variation in the choice of second line agents – likely driven by beliefs regarding efficacy of each agent compared to toxicity. For example, we know anecdotally that many Canadian pediatric nephrologists avoid using cyclophosphamide, a well studied and effective drug for frequently relapsing and steroid dependent nephrotic syndrome due to risk of infertility and cancer, and prefer using tacrolimus a less well studied drug with a more favorable side effect profile.[22,44] Therefore, understanding 'why there is practice

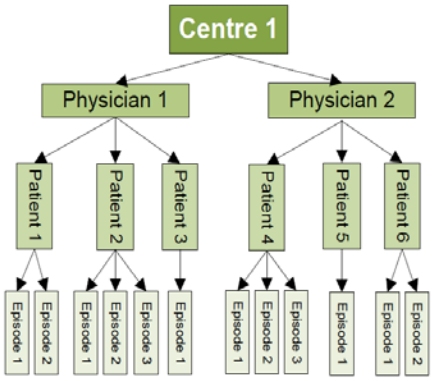
variation' is a key step to overcome barriers to implementation of best practice approaches across many centres. No study to date has assessed reasons for variation in nephrotic syndrome care.

2.6 There is uncertainty in the literature regarding best treatment protocols for childhood nephrotic syndrome. The evidence supporting many guideline recommendations for steroid therapy and second line agents are based on small numbers of randomized controlled trials (RCTs), some with very few patients – leading to lack of trust among the physician groups in the robustness of the literature.[44,45] In addition, the literature continues to evolve with conflicting messages. Three recent RCTs (2 in the same January 2015 Kidney International issue) were published; they all suggest that there is no benefit to prolonged steroid treatment of up to 6 months compared to 3 months for first presentation of nephrotic syndrome.[46-48] A recent editorial published with these new RCTs suggest that future trials should no longer just focus on duration of steroid therapy over the short term, but rather study emerging novel treatments for nephrotic syndrome and long term outcomes.[45] In the light of new evidence, and prevalent practice variation, we believe that a national observational cohort study is ***a necessary first step*** to obtain valuable generalizable data. These data will: 1) inform whether there is a need to develop standardized protocols to reduce practice variation by identifying differences in patient outcomes based on steroid prescribed; 2) provide observational patient outcome data to complement interpretation of published short term clinical trial results; and 3) assist in strategic prioritization of future clinical trial questions regarding new and old therapeutics.

2.7 We need a collaborative research network and data infrastructure to improve outcomes in childhood nephrotic syndrome, a rare pediatric chronic disease. Childhood nephrotic syndrome is one of the most common acquired kidney diseases in children, but, it meets the Canadian Institutes for Health Research (CIHR) definition of a 'rare' disease (affects one person out of 2,000 or fewer).[49] No single centre or region in Canada has sufficient patient numbers to produce generalizable knowledge regarding effective treatments, the most significant barrier to generating high quality evidence and one that can be overcome by multi-centre collaborative studies. Clinical research networks, with the combination of high quality data and large sample size accrual, are proven powerful tools to improve health outcomes of children with rare diseases. For example, the ImproveCareNow network for pediatric inflammatory bowel disease includes 445 pediatric gastroenterologists and 50 sites, and has seen remission rates for Crohn's disease and colitis improve from 49% to 78% in just 5 years.[50-52] For steroid sensitive nephrotic syndrome in particular, there is a severe lack of well characterized clinical and/or research cohorts. There is only one single-centre cohort study in Canada documenting outcomes of steroid sensitive patients (INSIGHT study, with a focus on genetic investigations)[53] – creating a major gap in knowledge regarding overall quality of clinical care and patients' clinical progression and outcomes. Funding this proposal will sustain a national network, composed of >20 investigators, with an estimated 50 physicians who will enroll from 13 sites, and establish the ***only*** national longitudinal observational cohort study for children with nephrotic syndrome.

2.8 Expected results and significance: We expect to observe differences in relapse rates based on steroid prescribed (Objective 1) and we expect to find that physician and centre characteristics play an important role in determining variation in treatment protocols (Objective 2). Our KT strategies will utilize the collective information gathered in this study regarding steroid prescribed and relationship to outcomes, and factors determining variation in treatments, to develop best practice approaches for treatment of nephrotic syndrome, and to identify physicians and centres most or least likely to implement these approaches. This project will also provide the unprecedented opportunity for every child with nephrotic syndrome and every physician treating children with nephrotic syndrome to be enrolled into the observational cohort, their data being used to inform development, implementation and iterative refinement of treatment protocols, and provide foundational clinical data to prioritize future clinical trials.

3.0 METHODS



We have conceptualized our study, evaluating clinical care and outcomes of childhood nephrotic syndrome, based on Donabedian's well known 'structure, process, and outcome' framework for health services evaluation.[54] Our work plan to achieve objectives 1 and 2 (to evaluate association of steroid dose prescribed with outcomes, and to understand sources of variability in treatments), using both quantitative and qualitative methods and a nested data architecture with patients' data linked to their physicians and physicians' data linked to their centres (see adjacent figure), will broadly address structure, process and outcome elements operating at three levels. First in section 3.1 below, we provide details regarding creation and characterization of the prospective cohort – the means by which we will achieve objectives 1 and 2.

3.1 Cohort Creation and Characterization

Population and setting: All children who present to pediatric nephrology clinics with a clinical diagnosis of nephrotic syndrome will be eligible for enrollment into the longitudinal cohort. All pediatric nephrology centres in Canada (n=13) are participating in this national study (see attached support letters). All pediatric nephrologists who care for children with nephrotic syndrome in Canada are eligible for enrollment.

Enrollment period: The enrollment period for the prospective cohort will last 4.0 years. The observation period will continue for an additional 6 months after the enrollment period (to ensure minimum 6 months follow-up for all patients by end of study).

Inclusion criteria: A patient is eligible to enter the cohort if he/she meets one of the following 2 criteria. See Appendix, Figure 1 for patient enrollment plan.

- A child with **first presentation** of nephrotic syndrome who meets the following criteria: age 1 to ≤17.5 years; edema present; urinalysis shows proteinuria (> 3+ on dipstick; > 3 g/L on urinalysis or urine protein to creatinine ratio > 200 mg/mmol); serum albumin < 25 g/L; and no prior treatment with steroids.
- A child with an established diagnosis of childhood nephrotic syndrome who presents at the beginning of either a **first or second relapse** (defined as proteinuria > 3+ on dipstick, > 3g/L on urinalysis or urine protein to creatinine ratio > 200 mg/mmol for 3 consecutive days) during enrollment period, prior to start of steroid sparing agents or kidney biopsy.

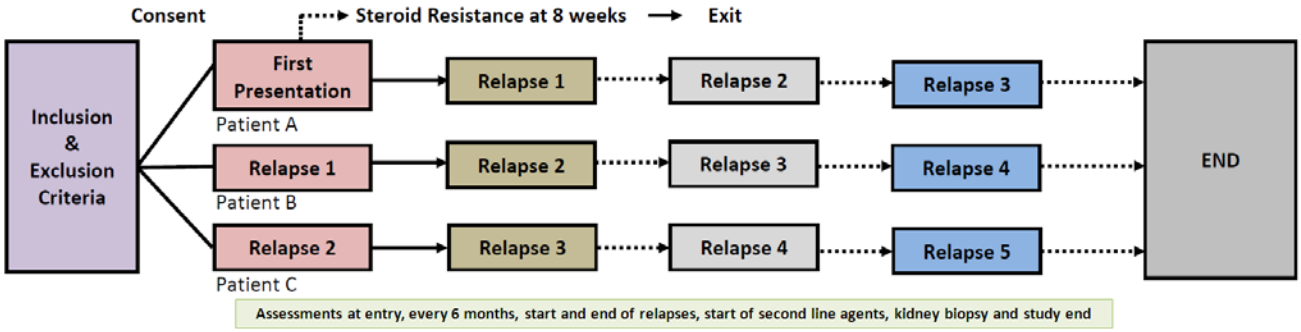
Exclusion criteria: Patients will be excluded if they meet one of the following criteria either at enrollment or during course of study: 1) secondary cause of nephrotic syndrome (e.g. lupus, malignancy); 2) C3 low suggesting high likelihood of secondary cause of nephrotic syndrome. Patients ultimately shown to be steroid resistant will be excluded from the final analysis, but will continue to be followed in the prospective cohort. Enrolled patients who turn 18 years of age during the study will exit the study. Further follow-up will be sought for these adult patients using a revised ethics application.

Patient enrollment: Two team members from each participating site will be primary contacts for the study (one physician and one nurse/research staff). Every 2 weeks these individuals will generate a list of patients seen with nephrotic syndrome by reviewing inpatient and outpatient data (clinic scheduling records) to determine eligibility. All patients with a clinical diagnosis of nephrotic syndrome who meet the inclusion and exclusion criteria will be introduced to the study by the primary treating physician. The site investigator will approach patient/parents to obtain informed consent and will also obtain assent from older patients (age >12 years). Patients will be enrolled in the study if they meet inclusion criteria and

their legal guardian has given informed consent. Consent forms will be available in English and French. Logs of all patients screened and consented, and for those who declined the reason will be kept.

Physician enrollment: Informed consent will be obtained from physicians within participating nephrology care teams to allow their demographic information (age, gender, location of nephrology training, years in practice) to be collected. Physician data will be linked to their patient's data in the nested data architecture. Once linked, physician identifying information will be removed. If a consenting patient's physician declines to participate in the study, the patient's data will be linked to a generic category of 'unknown physician.'

Patient data being collected: Study data will be collected at the following study points (see Figure below and more details shown in Appendix, Figure 2): 1) study entry (whether first presentation, first relapse or second relapse); 2) at the beginning of all subsequent relapses [defined as proteinuria > 3+ on dipstick, > 3g/L on urinalysis or urine protein to creatinine ratio > 200 mg/mmol for 3 consecutive days or start of full dose steroids (60 mg/m^2 or 2mg/kg)]; 3) at the end of first presentation and end of all subsequent relapses [defined as both remission of proteinuria – negative or <1.0 g/L protein on dipstick for 3 consecutive days, and off steroids]; 4) study visits every 6 months after entry; 5) at start of all steroid sparing agents; 6) at time all kidney biopsies; and 7) study end.



At entry, we will record demographic information (age, gender, ethnicity, family income, parental education, past medical history), height, weight, blood pressure, blood test results (C3, albumin, cholesterol, creatinine), urine protein values by dipstick (routine clinical practice is to use urine albumin dipsticks [Albustix™, Bayer], but urine protein to creatinine ratio will be recorded if available), medical history and details of steroid prescription. For patients entering at first or second relapse, demographic and treatment information regarding first presentation and/or first relapse will be collected using retrospective chart review when available. We will allow for enrollment up to second relapse (lengthening time interval to obtain consent) in order to maximize patient recruitment. Standardized assessments by physicians will be performed at the following study points: study entry, semi-annual study visits, and at study end.

Data for study points will be obtained using one or all of the following methods: chart review, reviewing patient log books of daily home urine protein measurements and steroid dose given, and phone calls to family to confirm details of clinical course (including date of proteinuria remission for each relapse). Logs maintained by patients are part of routine clinical care in nephrotic syndrome; all study patients will be provided with standardized log books for medications and relapse tracking. This schedule and method of assessments for study points were designed to mirror routine clinical care (as reported by most sites) and to maximize feasibility while maintaining ongoing engagement by study patients and physicians.

Defining an episode of treatment: As nephrotic syndrome is a relapsing and remitting disease, a significant portion of the study data will involve documenting treatment for both first presentation and

relapses of nephrotic syndrome (called 'episodes' in this study). Detailed steroid prescription information will be recorded at entry, and at the beginning and end of all subsequent episodes.

> An **episode** is defined as the time from start of full dose steroid therapy (60 mg/m^2 or 2mg/kg) to cessation of steroids or re-start of full dose steroids as in steroid dependent patients who relapse while tapering steroids.

The standard definitions used in nephrotic syndrome are provided in Appendix, Table 2. The data collection forms, shown in Appendix Figure 3, are designed to capture steroid prescriptions for each episode from the date of start of full dose steroid therapy (60 mg/m^2 or 2mg/kg) to cessation of steroid therapy or restart of full dose therapy. Each patient's steroid prescription for an episode will be linked to the prescribing physician.

Data quality and standardization: Standardized case report forms will be used for data collection regarding the clinical course, outcomes and treatments for childhood nephrotic syndrome. All patient and physician data will be entered by study staff into a multi-centre online database (REDCap™, a web-application which allows users to build databases securely for the purposes of research and in particular for longitudinal cohort studies, http://project-redcap.org/ hosted by Women and Children's Research Institute, Edmonton, see letter from Dr. Sandra Davidge). Data are being monitored weekly to address data quality issues in real-time. Based on the 77 subjects enrolled to date, we have confirmed that the majority of data to be collected for this study is recorded routinely by nursing staff in clinical care, and the web based system does not pose significant additional onerous data entry requirements.

The study will be coordinated centrally in Calgary. Two central study staff (study nurse and data analyst) will train all other site-specific study staff regarding study goals and objectives, data management and data entry. We put in place several measures to ensure data consistency and standardization including: piloting case report forms and standardizing forms; training site staff for data element definitions; using a data dictionary; establishing inter-rater reliability for data entry using two study staff at each site at start of study; and pre-study patient visit planning to standardize data collection and entry. Every 3 months, data analyst will review data entry completeness for individual patients and send reminders to appropriate site investigators for data completion. There will be a 2 step review for data completeness for each patient record – first by the data analyst and second by a lead investigator or designate. Data are time-stamped as complete after review. Key measures of data quality were identified a priori; a sample data quality report is attached in Appendix, Tables 3 and page 16.

Privacy and confidentiality: We will assign unique study numbers to patients, physicians and centres – to protect anonymity of all participants and centres. All identifying information will be securely stored at individual sites and will not be shared with central study staff.

Characterizing the cohort: We will describe (using means with standard deviation, medians with interquartile range and proportions as appropriate) the cohort demographics, and all outcomes of interest by centre-, physician, and patient- level variables. We will describe the following outcomes: overall steroid prescribed (total dose and number of treatment days), time to first relapse, relapse rate during observation, time to steroid sparing agents, choices of steroid sparing agents and indication, time to kidney biopsy, reasons for biopsy, complications of steroid therapy. Outcomes related to complications of steroid treatment will include: anthropometric changes during observation period (age- and sex-specific standard-deviation scores (z scores) for height, weight, and body-mass index); persistent systolic/diastolic blood pressure $\geq 95^{th}$ percentile during observation period [yes/no] and requirement for antihypertensive therapy [yes/no] and duration of therapy; and external manifestations of steroid toxicity evident during semi-annual study visits (Cushingoid faces [yes/no], hypertrichosis [yes/no], cataracts [yes/no], striae [yes/no], acne [yes/no]). Definitions of external manifestations of steroid toxicity are

similar to those observed in prior nephrotic syndrome steroid dosing studies.[38] See Appendix, Table 4 for detailed description of these variables.

3.2 Work plan for objective 1

Design: To determine the association of steroid dose prescribed with relapse rates, we will use the prospective cohort as described in section 3.1. We hypothesize that increasing steroid dose prescribed per unit time will be associated with decreasing relapse rates. All patients with steroid sensitive nephrotic syndrome enrolled into the prospective cohort will be eligible for this study. The observation period will span a maximum of 4 years and minimum of 6 months. Figure 4 in the Appendix provides a visual representation of the outcome and exposure as defined below for this objective.

Outcome: The primary outcome of interest is relapse rate (number of relapses/per person unit time). Relapse rate is the most clinically relevant outcome for nephrotic syndrome and the best indicator of morbidity experienced by patients; this outcome definition is consistent with prior literature in this area.[40]

Exposure: The exposure is steroid prescribed per unit time - that is the total dose patients were prescribed as treatment for episodes of proteinuria divided by the sum of duration of 'days on steroids' during observation period. Days on steroids is defined by the sum of the length in days of all episodes (see definition of episode in section 3.1, also graphically represented in Appendix Figure 4) observed. This definition is consistent with measures of steroid exposure used in prior nephrotic syndrome steroid dosing studies conducted in Europe and in a Canadian study of steroid associated osteoporosis in children.[38,55] Systemic steroid exposure (both oral and intravenous) will be converted into prednisone equivalents (mg/m^2) using standard dose conversion tables and weight based dosing criteria [mg/kg] will be converted to mg/m^2.

Analysis plan: The unit of analysis is the patient. Given that the main outcome of interest is relapse rate, we will use Poisson regression models with steroid prescribed per unit time as the exposure and relapse rate per unit time as the outcome, adjusting for patient level variables (age, gender, ethnicity, household income, parental education) and episode at entry into study (either first presentation, first relapse or second relapse), and taking into account time at risk. We are not using multi-level (hierarchical) analysis in this objective, as there is no clustering at the patient-level. There is only one measurement per patient, relapse rate adding all episodes experienced by one patient as a count.

Feasible sample and power considerations: We estimated a feasible sample based on data gathered from 2 sources: an ongoing longitudinal study of children with nephrotic syndrome (INSIGHT study, led by Dr. R. Parekh) recruiting a Toronto based cohort,[53] and our preliminary data (Appendix Figure 5 for preliminary recruitment rate). Based on the expected consent rate of 72%, and estimated drop out of 10% (due to loss to follow-up or steroid resistance), we estimate that we will be able to enrol and follow, at least, 520 patients over a period of 4.0 years (65 patients every 6 months). In our preliminary work, we have already enrolled 77 patients from 6 sites, thus our total estimated sample is 597 patients.

Although we hypothesize that increasing steroid dose prescribed per unit time will be associated with decreasing relapse rates, no studies to date have reported a specific magnitude of the effect of steroid prescribed per unit time on relapse rates. A systematic review of available clinical trials examining this issue, published in 2007, only reports on risk ratios based on the dichotomous outcome of any relapse at a pre-specified time interval (usually 12 or 24 months).[40] Our outcome of interest is an actual rate (count of relapses/person years). Hence, a power based, effect size dependent sample size calculation was not performed. At a significance level alpha = 0.05, and under the following assumptions of a mean daily steroid dose of 30.64 mg/m^2 with a standard deviation (of the dose) of 8.85, a base rate of relapse of 1.68 per person year, average follow up (time at risk of relapse) of 2 years and a conservative correlation (R^2) of the steroid dose with other covariates of 0.2, we would have 90% power to detect an incidence rate

ratio of 0.989 or smaller (i.e. a larger effect size) in a multiple Poisson regression. We are allowing for a 2 tailed test to allow the possibility of the effect being on either side of the null.

3.3 Work Plan for Objective 2

Design: To determine the associations between centre-, physician-, patient-level characteristics and i) steroid dose prescribed, and ii) length of steroid treatment for first presentation and subsequent relapses of nephrotic syndrome, and to identify reasons for practice variation between and among pediatric nephrology care providers and centres, we will use a mixed methods approach as defined by Creswell & Plano Clark.[56] The primary study is a quantitative study using the prospective cohort as described. A qualitative study, serving a supplementary role, is embedded within the larger quantitative study to provide a deeper understanding of the complex multi-level processes that lead to practice variation between centres and between physicians within centres. True to qualitative approaches, no a priori hypothesis is specified for this aim. At the completion of quantitative and qualitative studies, we will use a convergent parallel mixed methods analytic approach (both quantitative and qualitative data collected and analysed during the same phase of research, then two sets of results are merged for an overall interpretation), to compare qualitative and quantitative data across centre-, physician- and patient-level attributes. The results of both components will inform the 'greater whole' - a comprehensive understanding of why there is variability in care for nephrotic syndrome – a key step to overcoming barriers to implementation of best practice approaches for treatment of nephrotic syndrome across Canada and to make future randomized controlled trials more feasible.

Description of the quantitative study: We will use the prospective cohort described in section 3.1 to determine the associations between centre-, physician-, patient-level characteristics and outcomes. All patients with steroid sensitive nephrotic syndrome and all physicians enrolled into the prospective cohort will be eligible for this study. We will use the hierarchical data in the prospective cohort. The observation period for this objective will be a maximum of 4.0 years and minimum of 6 months.

Outcomes: The primary outcome is steroid prescribed per episode. We will examine: a) total dose patients receive for an episode; and b) average daily dose by dividing the total dose by duration (in days) of the episode. Dose will always be in mg/m^2 prednisone equivalents. This outcome definition is consistent with measures of steroid exposure used in prior nephrotic syndrome steroid dosing studies.[38,55] We are evaluating steroid prescription per episode because in this objective, we will study determinants of variability in steroid prescription for episodes of proteinuria rather than patient outcomes related to cumulative exposure of steroids (e.g. relapse rate). All episodes will be categorized either as first presentation or relapse. The secondary outcome will be length of episode in days.

Exposures: Exposure variables of interest are categorized into centre-, physician- and patient-level variables. Centre-level variable is defined as existence of a standardized protocol within centre for treating first presentation and relapses (information will be obtained from the site investigator as existence of centre based protocols [yes/no]). Physician-level variables are gender, year of graduation from nephrology fellowship, and location of nephrology training (Canada vs. outside Canada). These centre- and physician-level variables were shown to impact variability in practice patterns according to our published survey.[22] Patient-level variables are age, gender, ethnicity, and status at entry into study (first presentation, relapse). These variables are further described in Appendix, Table 5.

Analysis plan: We will describe the primary and secondary outcomes according to each of centre-, physician- and patient-level characteristics with 95% confidence intervals. To study the associations of centre-, physician-, patient-level characteristics with the primary outcome (steroid prescribed per episode), we will use mixed effects models with fixed effects for centre (standardized protocols yes/no), physician (gender, years in practice, location of training), and patient (age, gender, ethnicity) characteristics and random effects to account for physicians clustering within centre, patients clustering

within physician, and episodes clustering within patients. We will create separate models to examine both total dose patients receive for the episode, and average daily dose by dividing the total dose by duration (in days) of the episode. The unit of analysis will be the episode. Each episode will be categorized as either first episode or relapse at the patient level in the same model. The same methodology will be used to study the length of episode in days (secondary outcome).

Description of the embedded qualitative study: The embedded qualitative study will enrich the quantitative results by providing detail regarding attitudes, beliefs and local factors driving variation in care - fundamental to understanding the complexity of health care professional decision-making.[57,58] Theoretically grounded in the *Ottawa Model of Research Use*,[59] we are conducting focus groups with health professionals who care for children with nephrotic syndrome to probe the reasons for variation in steroid protocols ('why do people do what they do'). Ten focus groups, one per site with 6-8 participants per group and each lasting 60 minutes, are planned. Informed consent will be obtained and participant responses will be anonymized. We are not requesting funds from CIHR for this study as we have completed 8 of these 10 focus groups; however, we have provided the interview guide and the preliminary results in the Appendix (pages 22-24) - as it is a critical component of our mixed methods design and KT plan.

Integration of quantitative and qualitative studies: We will independently analyze the qualitative and quantitative data using analyses for Objective 2 as detailed above. We will use a convergent mixed methods analytic approach to compare the results obtained in the quantitative with qualitative components (Appendix Figure 6), using matrices of the hierarchies of centre-, physician- and patient-levels and explanatory quantitative variables at each level and themes related to these same levels arising from the qualitative study (e.g., existence of standardized protocols in each centre, age and training background of the physician, patient's age and ethnicity; Appendix Table 6), asking whether two types of data are congruent or not.

Feasible sample and power considerations: For objective 2, there is no knowledge on expected effects from the explanatory variables on the outcome. Therefore, power calculations, which are based on having a specific alternative hypothesis, are not feasible. The analysis to be performed is a mixed effects model with three random effects (physicians within centre, patients within physicians and episodes within patients), for which there is no simple analytic formula to calculate the needed sample size. The innovative method of Monte Carlo simulation based on the number of subjects potentially available still needs to have as input the expected effects from each of the explanatory variables. In the case of this linear mixed model (for primary outcome), the effect of each variable is measured by its coefficient in the regression (for fixed effects) and by the estimated variance of the random effects. As justified in Objective 1, we expect a feasible sample of 597 subjects. Given this estimated enrollment number, and that we will have a total of 8 explanatory variables plus 3 random effects (estimated as parameters in the model), we are complying with the guideline of 10 observations (at the unit of analysis level) per variable.[60] As the unit of analysis will be the episode and an estimated 70% of patients will have more than one episode during the study, it is important to note that the 597 patients will yield from 597 to 1015 observations (episode at entry plus one additional relapse). This will ensure that estimates of random effects are feasible.

3.4 Summary of progress and preliminary results

With start-up funds obtained from CIHR and other sources, we launched the prospective cohort at 13 centres and have recruited 77 patients from 6 centres to date. The remaining 7 centres are either approved or close to full approval (ethics and contracts). All sites will be recruiting by June 2015 – demonstrating feasibility to complete the work plan as described in this proposal. Our preliminary data is provided in the Appendix. Baseline demographics of the patient and physician cohort enrolled to date are shown in

Tables 7 & 8. Preliminary data from the cohort demonstrating variation in steroid prescriptions by key patient demographic variables and by type of episode of treatment are shown in Tables 9a-c. Graphical representations of steroid prescribed per episode for different patient scenarios are shown in Figures 7a-d. Variation in steroid prescriptions between physicians within one site and variation in steroid prescriptions between sites are shown in Tables 10 and 11 respectively. We also show differences among patients in 'time on and off steroids' by site in Figure 8, and the average daily steroid dose over time by site in Figure 9. Finally, in Figure 10 and Table 12, we show differences in relapses (survival curve, and absolute relapse numbers) by site.

4.0 LIMITATIONS AND CONTINGENCY PLANS

There are several limitations of our work that must be acknowledged. Recruitment into the cohort study may be slow at times due to either seasonal variation in incidence of disease, or due to unforeseen site based challenges in recruitment. In the early phases of this study, we have demonstrated increasing recruitment rates. We will sustain recruitment by providing monthly enrolment reports, study reminders and scientific updates to site investigators. We will hold annual face-to-face investigator meetings to monitor study progress, build cohesion amongst members and solve any issues that may arise during the study. We may miss enrolment of patients living in non-metropolitan regions, particularly those who are managed by general pediatricians; however, we estimated this loss to be <5%. Contamination of treatment protocols may occur due to the study itself and resulting increased interactions between physicians within sites and between sites. We acknowledge that due to the national scope of this study, and its aims, we may influence practice over time; this is unavoidable and indicates the impact and novelty of the study. Furthermore as new evidence emerges such as the recent RCTs, practice may be influenced. To address changing practice over time we will monitor for and report this trend within the data. We may not capture all unknown confounders at centre, physician and patient levels despite our detailed data collection. For example, tracking patient adherence to steroid therapy would reduce some confounding due to non-adherence; such monitoring is beyond the scope of this study but will be part of our future work.

We also carefully considered potential areas where the analytic plan may fail to answer our research questions. We considered whether we will observe variation in care at all three levels in a relatively small patient sample and particularly small and potentially homogeneous physician groups. We are reassured by examining our preliminary data that even with fewer than a hundred patients, we are able to detect variation between sites, between physicians within centres, and within physician between patients. If we were to see homogeneity among physician groups within centres (e.g. cohesive physician groups with centre specific standardized protocols), we will reduce our model to two levels – centre and patient, if needed.

5.0 RESEARCH TEAM

We have assembled a strong and cohesive national team to ensure success of this project. We performed substantial collaborative work among Canadian pediatric nephrologists, from all 13 academic pediatric health centres in Canada, over the last 4 years, which has led to successful launch of this Project in August 2013. See list of project team members and progress at each site in Table 13 in Appendix. Key members of the research team and supporting infrastructure are described below.

Principal applicant: Dr. Susan Samuel is a Clinician Scientist at the University of Calgary. She is supported by salary awards from the CIHR Canadian Child Health Clinician Scientist Program (CCHCSP) and the Kidney Foundation of Canada Kidney Research Scientist Core Education and National Training Program (KRESCENT), with 75% protected time for research activities. She has

successfully led multi-centre collaborative health services research in pediatric nephrology using national administrative data; and has a proven track record in leading this project. [61-64]

Co-applicants: Dr. Nettel-Aguirre PhD, PStat, a biostatistician at the University of Calgary Department of Pediatrics, is overseeing the quantitative study design and all analytic methods. Dr. Shannon Scott, RN PhD from the University of Alberta is a national expert in child health, KT, and qualitative and mixed methods research. She is a Canada Research Chair (Tier 2) for KT in Child Health. As a co-applicant, she will advise on mixed methods approach, and guide KT activities. Dr. Michael Zappitelli from McGill University is Principal Investigator and co-investigator of multi-centre collaborative studies on pediatric acute kidney injury. Drs. Zappitelli and Samuel collaborated over the past 3 years to develop this project and will ensure its success over the next 5 years. Dr. Catherine Morgan (University of Alberta), Dr. Allison Dart (University of Manitoba), Dr. Rulan Parekh, and Dr. Cherry Mammen (University of British Columbia) are pediatric nephrologists and investigators trained in clinical epidemiology. They will provide oversight for the study, design data collection forms, recruit patients at their centres and be involved in data analysis and manuscript preparation. Dr. Allison Eddy, is the Chair of Pediatrics at the University of British Columbia and is an international expert in nephrotic syndrome.[1] She will advise the study team, assist in KT activities both nationally and internationally.

Supporting national infrastructure: We will receive mentorship and support from the Canadian Kidney Knowledge Translation and Generation Network (CANN-NET; www.cann-net.ca), a CIHR funded national network promoting best practices in nephrology. We will also receive support from the Maternal, Infant, Child, Youth Network (MICYRN). See attached letters from Dr. Braden Manns and Dr. Anne Junker.

6.0 KT PLAN

Integrated KT plan: We are using an integrated KT model wherein decision-makers and end-users (pediatric nephrologists and parents) are engaged at all stages of the research process from priority setting and identification of key questions to interpretation and dissemination of results. [65,66] The involvement of decision-makers and end-users throughout will be critical for the success of the research aims and to ensure efficient and timely data collection at all participating centres.

For all 13 Canadian pediatric nephrology centres, we have identified site investigators (see letters of support attached) who are acting as local champions for this Project. We also have strong support from the leadership of Canadian Association of Pediatric Nephrologists (see letter from Dr. Maury Pinsk, President). The Association has provided several opportunities for us to engage pediatric nephrologists at semi-annual meetings and will also assist with our KT plan.

We have recently engaged committed parents, from different geographical regions and backgrounds, who are willing to partner with the study team to ensure patients and families are engaged in KT and that patient and family priorities are addressed in the future directions of this national initiative (see support letter from Ms. Andrea Galbraith, parent of child with steroid sensitive nephrotic syndrome). We will host at least 2 parent group teleconferences over the next 6 months to educate parents and/or patients about this national research initiative, our study plan and to learn from them about the daily challenges that they face, and how research might inform these. We envision that this will lead to a long-term meaningful engagement in KT and dissemination activities during this course of this study.

We are holding face-face to investigator and team meetings yearly in conjunction with the Canadian Society of Nephrology annual general meeting. We will also host a Canadian Childhood Nephrotic Syndrome Project Symposium on September 17 and 18 of this year in Calgary – to plan for the next steps and sequential building blocks in our research program. The symposium will bring together the national study team, both local and international experts, as well as basic and translational researchers

working in this area, in order to foster creativity and innovation through trans-disciplinary collaborations. The parent group will be invited to participate in this symposium and we will also use this opportunity to conduct a semi-structured group interview to elicit patient/parent priorities and ensure that these priorities align with our work plan for the future. We have applied for a CIHR planning and dissemination grant to fund this meeting.

In the final year of funding, all stakeholders (investigators, principal knowledge users, site investigators from all 13 sites, and invited experts including representation from parent/patient groups) will be invited to a face-to-face meeting to assist in the interpretation of study results. Both the quantitative and qualitative results of the study (description of cohort, clinical course including steroid exposure and use of second line agents by centre, physician and patient variables, association of variability in steroid treatment on relapse rates, results of multi-level mixed methods models showing factors significantly associated with variation in steroid treatment, and common themes regarding variation in care elicited from focus groups) will be presented. All clinical practice guideline recommendations will also be reviewed. Utilizing all this information, we will draft best practice approaches for treatment of first presentation and subsequent relapses of nephrotic syndrome acceptable to all stakeholders. We will develop an implementation plan, informed by results of Objective 2 (centre-, physician- and patient-level characteristics driving variability in care), and ensure that the comprehensive results of this study are disseminated to physicians and other relevant stakeholders within each centre.

End-of-grant KT plan: We published our study plan in the new journal of Canadian Journal of Kidney Health and Disease (Samuel et al. 2014, see attached manuscript). Our next manuscript will describe the results of the qualitative study (target completion date June 2015). The remainder of our manuscript plan - to disseminate the quantitative and mixed methods results are detailed in the Appendix page 38, Gantt chart. We will present our findings at local (nephrology divisional rounds and pediatric grand rounds with telehealth connections to rural sites and primary care pediatrics offices), national (Canadian Society of Nephrology and Canadian Pediatric Society meetings) and international (American Society of Nephrology meeting, special interest group meetings for pediatric nephrology). The Principal Applicant, co-applicants and site liaisons are members of these organizations and will ensure effective and prompt dissemination of research findings to relevant knowledge user groups locally, nationally and internationally.

7.0 SUMMARY AND SIGNIFICANCE

Funding the Canadian Childhood Nephrotic Syndrome Project will address important unanswered questions in childhood nephrotic syndrome – what is the impact of variability in steroid treatments on patient outcomes (Objective 1) and who and what drives variability in care (Objective 2)? The integrated results of the study will allow us to develop best practice approaches for treatment of nephrotic syndrome and to develop an implementation plan to ensure uptake of our study results nationally and internationally. This study will provide key information to strategically prioritize future clinical trial questions (what to study, in which patients, when, and how to get buy-in from key stakeholders), and will build basic research infrastructure needed to conduct these trials to address critical knowledge gaps in the treatment of nephrotic syndrome. The novel national longitudinal web based patient data collection system developed as part of this study will also provide a platform to evaluate clinical care and outcomes on an ongoing basis in the future, and ultimately create a best practice approach to treatment of nephrotic syndrome.

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