CureGN: Cure Glomerulonephropathy Network

Core Study Protocol

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Study Sponsors: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	
INSTRUCTIONS: The Principal Investigator must print, sign, and date below. The original signature page should be kept in the site's records. After signature, please scan the signature page and email or fax to the CureGN DCC at the address listed below: CureGN-ProjectManagement@med.umich.edu	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 45, 50, 56, and 312. Further, I will conduct the study in keeping with local, legal, and regulatory requirements. As the Principal Investigator, I agree to conduct and to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the CureGN Steering Committee.	
Site Principal Investigator (Print)	
Site Principal Investigator (Signature)	
Date	

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	
AE	Adverse event
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CMS	Centers for Medicaid and Medicare Services
CRF	Case Report Form
CureGN	Cure Glomerulonephropathy
DCC	Data Coordinating Center
DPR	Digital Pathology Repository
eGFR	Estimated glomerular filtration rate
EHR	Electronic Health Record
EM	Electron microscopy
ESKD	End stage kidney disease
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IgAN	Immunoglobulin A nephropathy
IRB	Institutional Review Board
ITS	Information Technology & Services
MCD	Minimal Change Disease
MN	Membranous Nephropathy
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
OSMB	Observational Study Monitoring Board
PCC	Participating Clinical Center
PHI	Protected health information
PLA2R	Phospholipase A2 receptor
PRO	Patient reported outcomes
RRT	Renal replacement therapy
QC	Quality control
SAE	Serious adverse event
sIRB	Single Institutional Review Board
UPCR	Urinary protein: creatinine ratio
V0	Enrollment Visit
WHO	World Health Organization

INTRODUCTION

Glomerular disease, including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and immunoglobulin A nephropathy (IgAN), often share a common clinical presentation. These chronic diseases, affecting both children and adults, result in proteinuria, hypoalbuminemia, hematuria, and/or edema, as the glomerulus is damaged by the underlying disease process. Progressive loss of kidney function often occurs over many months or years and results in substantial individual and societal burden.

There exist several major challenges to understanding the underlying biology of these conditions and to translating that understanding into effective therapies for patients. These include the fact that glomerular diseases are a relatively rare cause of chronic kidney disease (CKD) as compared with more common etiologies such as diabetes, hypertension, or congenital anomalies of the kidney and urinary tract. The slow progression in many patients may require follow-up periods of decades to measure effectiveness of an intervention, as alternative endpoints to death and end stage kidney disease (ESKD) have not been definitively validated in this population. As a result, it is difficult to recruit sufficient numbers of patients to study underlying mechanisms, identify disease targets and biomarkers, and evaluate new therapies.

Cure Glomerulonephropathy (CureGN) is a multi-center consortium that works collaboratively to address these challenges through recruitment of a large, ethnically diverse cohort of glomerular disease patients and following them prospectively with a common protocol. This study has established an infrastructure enabling the following questions to be addressed for glomerular disease patients:

- What is this disease?
- Why do I have this disease?
- What will happen to me?
- What effective treatments can you offer me?

1. BACKGROUND AND SIGNIFICANCE

MCD, FSGS, MN, and IgAN are glomerular diseases which often result in devastating complications of nephrotic syndrome and progressive renal insufficiency. Although relatively rare compared with the most common causes of CKD, they present a significant individual and societal burden. The morbidity and mortality from these diseases are related both to complications of the disease itself (e.g., ESKD, venous thromboembolism[1,2], bacterial peritonitis[2], hypertension, symptom burden, and reduced quality of life[3,4]) as well as the immunomodulatory therapies (e.g., steroid toxicity[5], calcineurin nephrotoxicity[6], impaired fertility[7] and bladder toxicity of cyclophosphamide[8], and infectious complications). In 2010, glomerular diseases accounted for 13% of ESKD prevalence (84,521/640,023 patients) in the United States[9]. Among patients <20 years old, FSGS is the leading cause of acquired ESKD. Furthermore, IgAN is the leading cause of primary glomerular disease and an important contributor to kidney failure worldwide[10].

Although these glomerular diseases are currently categorized as four distinct histopathologic categories, they result from multiple biological mechanisms. At the same time, their clinical phenotypes cross these four histopathologic categories and are treated with common therapeutic strategies. In the current treatment paradigm, diagnostic, prognostic, and therapeutic decisions are largely based on histological and crude clinical parameters that do not account for the heterogeneity of the biological antecedents and disease trajectories. As a result, available therapies are few, and individual response uncertain. Progress has been limited by the rarity of these diseases and long duration of observations required to evaluate clinically relevant outcomes such as kidney failure and death. As a result, many current treatment recommendations are based on retrospective data, small numbers, and heterogeneous study populations[11]. Thus, we are challenged to provide specific, individualized treatments for people with glomerular disease.

Novel insights into pathophysiology of these disorders have been described recently. Anti-phospholipase A2 receptor (PLA2R) antibodies have been identified in approximately 70% of idiopathic MN cases in adults and may serve as an important marker for diagnosis and disease activity, as well as potentially a therapeutic target[12]. Multiple other autoantibodies have now been identified in idiopathic and secondary MN cases[13]. Autoantibodies to nephrin have been

described in both MCD and FSGS[14]. Antibody-antigen complex stimulated by aberrant IgA1 O-glycan has been identified as a pathogenic mechanism in IgAN. Genetic studies of primary glomerular diseases have identified specific genetic risk loci associated with disease, disease-specific phenotypes, and risk of both progression to ESKD and post-transplant recurrence[15-19]. In parallel to the disease-specific advances, we are engaged in a fundamental transition from research models focused on the functions of single molecules or pathways to an integrative biology analyzing biological systems as a unified whole. This systems biology approach integrates genome-scale data sets to define key drivers of diseases and allows the formation of novel hypotheses of organ function and failure[20].

A key underlying hypothesis of CureGN is that different glomerular disease mechanisms can result in similar histological and clinical phenotypes, but very different disease courses. A similar hypothesis has been extensively evaluated in oncology. Comprehensive molecular analysis of tumor tissue has allowed the definition of cancer-specific molecular fingerprints representing different disease mechanisms or states of classically indistinguishable neoplastic lesions[21,22], with some currently under prospective evaluation as prognostic and predictive biomarkers[23]. The application of a similar strategy to glomerular disease will allow a mechanistic disease definition and, we believe, will have far-reaching consequences for diagnostic classification, prediction of disease and risk of progression, definition of patient cohorts for clinical trials, and identification of personally tailored therapeutic regimes[21].

To accomplish these goals, the CureGN consortium will continue to recruit and maintain a large cohort of patients with glomerular disease and follow them prospectively with standardized clinical data and biospecimen collection. The infrastructure and study design presented in this protocol will form the backbone for a broad range of scientific approaches and inquiries, essential to moving the field forward and improving the outcomes of patients affected by these diseases.

2. AIMS

2.1. CUREGN CONSORTIUM AIMS

Aim 1: Support the logistical infrastructure of the CureGN Consortium in pursuit of its core scientific aims to enable the performance of transformative translational research.

Aim 1a: Implement efficient consortium organization to accomplish overarching study goals including scientific productivity, communication, and community engagement.

Aim 1b: Maintain harmonized oversight, training, and regulatory processes to ensure highest standards for clinical study execution across the international CureGN network.

Aim 1c: Engage junior investigators in all consortium activities, including scientific output.

Aim 1d: Engage and promote participants as research leaders through a robust Patient Advisory Council, outreach through mobile health technologies, and partnership with patient advocacy groups to ensure diverse patient participation.

Aim 2: Continue the prospective observational study of children and adults with MCD, FSGS, IgA, and MN using efficient study administration procedures and modernized data and sample collection.

Aim 2a: Retain and recruit-to-replace adults and children using remote and in-person study visits, with focus on key subsets including populations typically underrepresented in research.

Aim 2b: Capture and integrate high-quality data including clinical, social, environmental, and other domains through multimodal data collection methodologies including electronic health record extraction, linkage to other databases, and participant-engaged mobile health technology.

Aim 2c: Ensure CureGN biospecimen capture and biobanking meet current and future investigator needs, including expansion of the comprehensive digital pathology repository and initiation of a formalin fixed, paraffin-embedded tissue block repository.

Aim 3: Advance state-of-science studies leveraging emerging technologies to define novel disease features and underlying biology for precise disease characterization, prognosis, and treatment strategies.

Aim 3a: Foster pilot and ancillary studies of innovative, high-quality, multi-disciplinary investigations, including collaborations outside the CureGN network and with nonprofitnon-profit and industry partnerships.

Aim 3b: Provide leadership for consortium-wide projects to understand remission, response to therapy, the role of the exposome, and how social determinants of health impact glomerular disease occurrence and outcomes.

Aim 3c: Facilitate key ancillary research themes through workgroups composed of experts in basic, clinical, and translational methods and integration of multi-domain data including clinical, histopathologic, genetic, epigenetic, immunological, metabolomic, and exposomics domains to advance the overarching goal of precision medicine approaches in glomerular disease.

2.2. SCIENTIFIC AIMS

The following Scientific Aims describe four broad categories of research that CureGN will address. The Aims are not exhaustive but establish over-arching goals that guide the study design, eligibility criteria, visit schedule, sample collection efforts, and eventual integration with ancillary studies. Each Aim will be addressed for each of the target CureGN diseases: IgAN, FSGS, MN, and MCD.

Aim 1 (Epidemiology). To describe the disease trajectory under current clinical care; to estimate event rates for clinically meaningful outcomes; to identify patient characteristics (demographic, clinical, laboratory, environmental) associated with glomerular disease and non-renal complications of disease; to identify clinical predictors of short- and long-term outcomes, including therapeutic response; and to evaluate intermediate outcomes, such as proteinuria, as potential surrogates for longer-term outcomes.

Aim 2 (Biomarkers). To identify and characterize clinical, histological, molecular, and genetic biomarkers that are linked to glomerular disease, disease outcomes, or that might be used to improve disease classification; to identify and characterize biomarkers that may be employed in clinical practice or clinical trials to predict disease trajectory, disease activity, or response to therapy.

Aim 3 (Genetics). To understand the genetic architecture of the four glomerulopathies, including studies of germline sequence variation, somatic mutations, epigenetic changes, and transcriptomic profile, and their impact on disease presentation and clinical outcome; study gene-gene and gene-environment interactions that contribute to the development of the four glomerulopathies; and devise systems genetics approach to clarify pathogenesis.

Aim 4 (PROs). To identify Patient Reported Outcomes (PROs, e.g., symptom burden, physical function, quality of life) associated with primary glomerular diseases; to validate disease-specific instrument(s) to assess the impact of disease and its therapy on patients; and to test the associations of PROs with disease progression.

3. INVESTIGATION PLAN

3.1. STUDY METHODS

3.1.1. OVERVIEW

The CureGN study is a multi-center prospective cohort study of approximately 2,800 adult and pediatric (<18 years of age) patients with biopsy-documented IgAN, FSGS, MN, and MCD. The protocol described below will maintain an active glomerular disease cohort of approximately 2000 active participants that is positioned to support current and future research. Participants will be recruited concurrently from each of the four Participating Clinical Center (PCC) networks: Columbia University, Pediatric Nephrology Research Consortium, University of North Carolina, and University of Pennsylvania. Each PCC represents multiple clinical sites, with current representation in the United States, Canada, Italy, and Poland. Participants meeting the criteria below will be enrolled if they or their legally authorized representative(s) provide signed informed consent, e-consent, and assent where applicable. Participants will be followed until death, withdrawal from the study, or end of study. Participant recruitment may occur at any point during the study period and will continue for all disease

groups to maintain the active cohort until the Steering Committee directs the network to close recruitment in one or more groups.

3.2. PARTICIPANT SELECTION

3.2.1. INCLUSION CRITERIA

- Diagnosis of MCD, FSGS, MN, or IgAN on first diagnostic kidney biopsy, as per specified pathology definitions
- First diagnostic kidney biopsy within 5 years of study enrollment
- Access to first kidney biopsy report and/or slides
- All ages
- Willingness to comply with study requirements, including intention to fully participate in protocol-specified follow-up at a clinical study site
- Informed consent and, where age appropriate, informed assent

3.2.2. EXCLUSION CRITERIA

- ESKD, defined as chronic dialysis or kidney transplant
- Institutionalized patient
- Solid organ or bone marrow transplant recipient at time of first kidney biopsy
- Diagnosis of any of the following at the time of first diagnostic kidney biopsy:
    - Diabetes mellitus (except gestational or diet controlled)
    - Histopathologic findings of diabetic glomerulosclerosis
    - Systemic lupus erythematosus
    - HIV infection
    - Active malignancy, except for non-melanoma skin cancer
    - Active Hepatitis B or C infection, defined as positive viral load

3.3. SCHEDULE OF VISITS, TESTS, AND ASSESSMENTS

3.3.1. VISIT SCHEDULE

Table A provides a schematic of the visit schedule. After consenting to CureGN, the first visit is the enrollment visit, denoted as V0, and is an in-person visit. Following the enrollment visit, CureGN years one through three visit schedule begins and includes one in-person visit and two remote visits (e.g., by phone, email or text) each year. The annual visit will be conducted in-person (Priority 1). If this is not feasible, remote visit via phone or email can be substituted (Priority 2). Starting in the fourth study year, participants will have one in-person, and one remote visit each year. The visits in years one through three should be spaced approximately four months apart, with the in-person visit occurring at any point during the year. Starting in the fourth year of participation, the visits should be spaced approximately six months apart. In addition, an in-person "relapse" visit may be conducted once per year. The relapse visit may take place at any point during the year and may either replace a scheduled in-person or remote visit or be an extra visit.

TABLE A: VISIT SCHEDULE

Visit Type	Enrollment	Year 1		Year 2		Year 3		Year 4+
Annual In-Person	X	X		X		X		X
Remote Interval Visits		X	X	X	X	X	X	X

3.3.2. ELIGIBILITY ENCOUNTER

For eligible patients, this will serve as an introduction to the CureGN study. This encounter may occur by phone or in-person. It may occur prior to, or at the same time as the in-person enrollment visit (V0). The study coordinator will confirm eligibility, review study requirements, and determine the participant's willingness to participate in the study. Informed consent may be obtained at this time or during V0.

3.3.3. ENROLLMENT VISIT

3.3.3.1. CONSENT

Prior to any research related procedures being performed, comprehensive informed consent, and if assent applicable, must be obtained from the study participant or their parent/guardian. A study team member will review and explain necessary information with the potential participant in accordance with the requirements of the Institutional Review Board (IRB) and federal human subject research regulations. For some portions of the study, including a mobile health application enrollment if available, additional consent may be required. We will obtain signed documentation for permission to collect medical records from previous or future healthcare providers using a HIPPA waiver and release of information forms. Remote electronic consent with an instructional video may also be used. Consent may take place prior to the enrollment visit.

3.3.3.2. PATHOLOGY REVIEW FOR ENROLLMENT

Participants may proceed with V0 prior to review of the kidney biopsy by the CureGN study pathologists if the physician investigator and/or the study coordinator believe that the participant meets eligibility criteria. Participants will be withdrawn from the study if biopsy review by a CureGN study pathologist reveals that the participant does not meet pathology inclusion criteria. Confirmation of diagnosis and assignment into diagnosis category (MCD, FSGS, MN, and IgAN) is accomplished at each PCC by a PCC pathologist via review of the participant's de-identified, uploaded biopsy report.

3.3.3.3. DATA COLLECTION

At V0, clinical data will be gathered by participant interviews, participant questionnaires, and chart extraction. The visit will include a brief focused physical exam, PRO measures, and biospecimen collection. Core clinical labs, including serum creatinine, serum albumin, and urine protein/creatinine ratio (UPCR) will be extracted from standard of care labs and recorded during study visits, by EHR linkage, or by manual extraction, if necessary.

3.3.3.3.1. PARTICIPANT ASSISTED DATA AND BIOSPECIMEN COLLECTION

Multiple data collection methods will be available for participants. We may utilize a mobile application that allows participants to link electronic health records (EHR), complete surveys, and access a dashboard etc. Additionally, participants may be offered a device for self-collection of biosamples. Finally, a contracted third party biosample or biospecimen collection method may be employed. We may offer participants the ability for a fully remote study visit performed by a vendor as contracting becomes available. More details about these collection methods can be found in section 3.3.5.

3.3.4. FOLLOW-UP VISITS

3.3.4.1. ANNUAL VISITS

In year one, annual visits will be conducted in-clinic, in-person. Starting in the second year, in-clinic visits are the first priority and remote visits via email or phone will be the second priority. Coordinators have the option to choose between indicated alternative data collection methods, adhering to priority rank order as indicated. Biospecimen collection in year 2+ may be done by in person collection, or collection by a third-party entity as available by the study.

3.3.4.1.1. PRIORITY1: IN-CLINIC VISITS

At this visit there will be data collection, as outlined in Table C, a brief focused physical exam, PRO measures, and biospecimen collection. In addition to a spot urine collection, participants who are able should collect a first morning void prior to the visit. First morning void can also be collected at a later visit and sent to the clinical site. Chart abstraction should be conducted to complete clinical data collection.

3.3.4.1.2. PRIORITY 2: REMOTE VISITS

Participants who are unable to come into the CureGN site for an in-person visit may choose to complete their CureGN annual visit remotely. Remote visits will maintain connection with the participant, ascertain major clinical events (e.g., interval ESKD, hospitalizations, relapse, and medication changes, etc.) and collect PRO data. Remote visits may be conducted by phone, email, mobile application, or other means. PRO measures may be completed via secure email link or using a mailed and returned paper version, per participant preference.

3.3.4.1.3. PRIORITY 3: CHART ABSTRACTION

Chart abstraction should be conducted to complete clinical data collection. If a participant cannot be contacted, a chart abstraction should be done to collect available clinical data. If information needed to complete a remote visit is only available in external medical records, a consent for release of medical information will be requested of the participant/guardian.

3.3.4.2. INTERVAL VISITS

Study participants will have two interval visits in each year of their first three years of participation in CureGN, and one interval visit per year starting in their fourth year of participation. All interval visits will be conducted remotely by phone, email, text, or other means. Remote visits will obtain clinical data by interview and/or chart abstraction and collect PRO data.

3.3.4.3. FOLLOW-UP AFTER ONSET OF ESKD

If a participant reaches ESKD, an in-person ESKD initiation visit with biospecimen collection will occur as soon as possible. After the in-person ESKD initiation visit, subjects with a kidney transplant should follow the standard visit schedule with annual in-person visits as shown in Table A. Subjects receiving chronic dialysis should follow the schedule in Table A, with the exception that remote visits will replace the annual in-person visits. Chronic dialysis patients who receive a kidney transplant should switch to yearly in-person visits, and transplanted persons reverting to chronic dialysis should switch to remote visits only. Participants with ESKD should be followed until death, withdrawal from study, or end of study.

Routine data collection for ESKD patients will be augmented with ESKD-focused data, including date of ESKD, renal replacement therapy (RRT) modality, date(s) of kidney transplant, donor type, and kidney disease recurrence.

Biospecimens collected at in-person visits (blood and, if possible, urine) should be procured and processed in accordance with the standard in-person visit.

3.3.5. BIOSPECIMENS

Total blood and urine volumes at enrollment, annual, and interval visits are listed in Table B below. Pediatric participants' blood volumes are based on weight at the time of the visit.

TABLE B: BIOSPECIMEN VOLUMES

	Total Blood Volume (ml)			Total Urine Volume (ml)	
Visit type	Enrollment (V0)	Annual Visit (In Person or Remote)	TAP Device	Enrollment (V0)	Annual Visit (In-Person or Remote)
Pediatric participants					
<21 pounds	21	15	0.9	80	20
21-<52 pounds	46	15	0.9	80	20
≥52 pounds	48	30	0.9	80	20
Adult participants	50	30	0.9	80	20

3.3.5.1. LOCAL LABORATORY TEST RESULTS

Laboratory results including blood chemistries, coagulation studies, hematology studies, urine studies, and rheumatologic/infectious serologies will be abstracted from the medical record as available.

3.3.5.2. CORE CLINICAL LABS

Core clinical labs (serum creatinine, cystatin-C, and albumin and urine protein:creatinine [first morning sample if available]) will be obtained from the medical record three times a year from years one through three, twice year in years 4 and 5, and then once a year starting with year 6. Data will be abstracted from the medical record as available. If participants are not getting core clinical labs done as based on their visit schedule, blood and urine may be self-collected as described below.

3.3.5.2.1. REMOTE SELF COLLECTION OF CORE CLINICAL LABS

Participants may choose to supplement remote visits with at-home self-collection of biospecimens, if offered by their site. Pre-assembled kits will be shipped to the participant by the TAP Coordinating Center, at Northwell Health, including one container for urine collection. The participant will be instructed to use the device to collect one cryovial of blood and one vial of urine from a first morning urine. Pediatric participants will be asked to provide a clinic (within 3 months) height and weight, or values measured at home by a parent/ guardian, to calculate eGFR.

Pertinent participant information needed to ship and return blood and urine collection materials will be shared with the TAP Coordinating Center at Northwell. Identifiable data will only be shared for patients who are eligible and agree to remote self-collection of labs. Biospecimens will be shipped to a central site by the participant using a pre-paid shipping label. The central labs will measure serum creatinine, albumin, and cystatin-C, and urine protein:creatinine ratio.

Blood Collection: The TAP Micro Select[â] (YourBio Health, Medford, MA) is a self-administered blood collection device that is FDA 510(k) cleared. The device uses microneedles and vacuum to assist in the collection of capillary blood for clinical laboratory assessments. The device is intended for use on the arm (or thigh for smaller individuals) and is reported to be virtually painless. Effective and safe use of the device has been demonstrated in large clinical trials including infants, children, and adult populations 24-27 and is considered non-significant risk. Reliability studies have compared TAP Micro Select[â] with traditional clinic venipuncture and have demonstrated good TAP-venous blood concordance. Participants will be provided with an instruction sheet and instructional video on how to collect a blood sample using the TAP Micro Select[â] device.

Urine Collection: Participants will collect a first morning urine sample in the urine container and will transfer urine into the vial by pushing the vial into the integrated transfer port and holding in position until the flow stops (10-20 ml). Participants will be provided with an instruction sheet on how to collect a urine sample.

3.3.5.3. BIOSPECIMENS FOR BIOREPOSITORY

Biospecimens will be collected for storage in the biorepository at the enrollment visit and at the year one in-clinic visit. Biospecimens will be collected annually from years 2 through 5 at in-clinic visits. Blood specimens, spot urine collection and first morning urine specimens will be obtained annually. For participants who are unable to collect a first morning void, a spot urine sample will be collected during the visit. Participants in study years 6+ who are not receiving standard of care labs may provide remote samples for central testing at the DCC through additional means including at home self-collection. If DNA/RNA is consented to and not collected at enrollment, it should be collected at the next in-person visit.

3.3.5.3.1. CONTRACTED THIRD-PARTY BIOSAMPLE OR BIOSPECIMEN COLLECTION

Select participants may be offered fully remote study visit performed by third party vendor nursing who would perform data collection and facilitate biospecimen collection via home or lab collection.

3.3.6. REMOTE MOBILE APPLICATION OR ELECTRONIC SURVEY

3.3.6.1. PARTICIPANT ENROLLMENT

We may ask participants to engage in a mobile health platform or mobile survey application for collecting patient reported data (PROs), linking electronic health records (EHR), and a patient facing dashboard, if available. The application can be accessed via iOS and Android mobile app stores and is also available via a website. Instructions (paper, e-mail, or verbal) will be provided to participants and study coordinators will be available to assist in the enrollment process. Emailed surveys and PRO's will also be an option in addition to traditional paper versions.

Following consent, participants will complete a small number of initial survey questions to ensure appropriate linkage can be made to the main CureGN study data which could include CureGN ID. Patient/guardian will be provided with an electronic way of enrolling in the electronic survey or mobile survey application via a mobile device or website.

Participants may choose not to enroll in the use of this application or limit their interaction with the application by not sharing EHR data through the application. These decisions will be communicated to the DCC study team and noted in the mobile survey application and case report forms (CRFs). Incentives will be available to patients as described in the patient payment section of the consent.

3.3.6.2. EHR DATA LINKAGE

Following enrollment in the mobile application, participants may be prompted to select all institutions where they receive healthcare from the current participating healthcare system list and subsequently login via their patient portal(s). If they do not have a patient portal established, a study coordinator will be available to help obtain portal access. As per individual institutional policies, participants will be allowed to choose data elements to share with CureGN. Participants will also be prompted to re-approve access as needed when initial permissions expire (if they do). For pediatric patients age, parent's proxy account portal linkage will be required. For adolescents, patient will be asked to provide linkage to EHR data with their own account with the assurance that all privacy procedures of adolescent care are adhered to.

3.3.6.3. ADDITIONAL IN-APP DATA COLLECTION

Data collection for PROs and other approved surveys will be offered to participants at up to a monthly cadence. Additional ad hoc surveys may be offered to participants for ancillary studies subject to IRB approval. Reminder notifications will be provided to complete surveys.

3.3.6.4. MOBILE APPLICATION WITHDRAW

Participants can withdraw from participation in the mobile application or e-survey portion of the CureGN study at any time through the application. As needed, the DCC will notify the sites of any withdrawn participants.

3.4. DATA ELEMENTS

Table C provides an overview of categories of data elements by visit type.

TABLE C: DATA ELEMENTS

Visit Type	Enrollment Visit	In-Clinic Visits	Remote Visits (phone, email, mobile application, other)
Demographic and Cohort Data			
Consent/Assent	X		
Demographics	X		
Census Tract	X		
Biopsy diagnosis/Pathology report	X		
Exclusion criteria	X		
Medical Data			
Comorbidities	X	X	X
Family history	X	X	X
Birth history	X		
Pregnancy history	X	X	X
Prior disease course	X		
Interim disease course		X	X
Medications	X	X	X
Hospitalizations	X	X	X
Kidney failure status		X	X
Vital status		X	X
Physical exam	X	X	
Vital signs	X	X	X
Patient Reported Outcome (PRO) Information[1]			
PRO questionnaire	X	X	X
Medication Adherence [Morisky-4]	X	X	X
Local Laboratory Test Results[2]			
Blood chemistries	X	X	
Coagulation studies	X	X	
Hematology studies	X	X	
Rheumatologic serology	X		
Infectious serology	X		
Urine studies	X	X	
Core Clinical Labs			
Creatinine, serum			X*
Cystatin-C, serum			X*
Albumin, serum			X*
Urine Protein:Creatinine			X*
Biospecimens for Biorepository			
Blood sample collection[3]	X	X	X
DNA and RNA collection[4]	X		
Spot urine sample	X	X	X
First morning void[5]	X	X	X
Pathology slides/images/tissue	X		

1. See Manual of Procedures for PRO and Medication Adherence measures
2. As available in the medical record
3. See Table C below and Manual of Procedures for Limited Lab Capacity specimen volumes and limited specimen collection and processing procedures for external biospecimen collection
4. If DNA/RNA is not collected at enrollment, it should be collected at the next in-person visit
5. If a participant is not able to collect a first morning urine, a random urine sample will be collected at the visit

*TAP Remote Biosample Collection

3.4.1. DEMOGRAPHIC AND MEDICAL DATA

At all study visits, demographics, medical history, family/birth/pregnancy history, prior disease course, hospitalizations and medication exposures will be collected. Additional information will include contact information, next of kin, information regarding participant's health providers, and signed documentation for permission to obtain medical records from previous or future healthcare providers.

Participant consent will include permission to link data to external data sources, such as Centers for Medicaid and Medicare Services (CMS) End Stage Kidney Disease (ESKD) data and National Death Index, for ascertainment of ESKD and vital status. It will also include permission to collect residential, school and work address and census tract location at enrollment. We will ask for participant's social security number (SSN) to link to these databases, if patient has a number available.

3.4.2. PATIENT REPORTED OUTCOME INFORMATION DATA

Participants will complete Patient Reported Outcomes (PRO) questionnaires at the enrollment visit, in-person visits and remote visits. The pros will take approximately 15 minutes to complete.

Self-report measures will be used for adults and children aged 8 years and older. Parent/guardian-proxies will complete the measures for participants aged 0-9 years of age. Ages 8-9 will have both parent proxy and patient PRO data.

There are novel PRO measures for patients with proteinuric kidney disease, items from the Patient Reported Outcomes Measurement Information System [PROMIS}, and the most troublesome symptom question. Redundancy in the questions is present to assist with the study objective to validate disease specific pros.

The Morisky Adherence Questionnaire will be completed by participants aged 8 and above and parent proxies of participants ages 0 through 9 years. Versions are available in English, Spanish, French, Italian, and Polish.

3.5. DIGITAL PATHOLOGY REPOSITORY

De-identified kidney biopsy glass and digital electron microscopy images will be collected from participants for whom slides/images are available. Glass slides will be scanned into whole slide images and deposited in the CureGN Digital Pathology Repository together with the digital electron microscopy images. The digital biopsy images will be used for pathology scoring and ancillary studies. Scanning of the glass slides into whole slide images may occur at the local pathology sites or at a central CureGN Scanning facility. Participants without available slides may still be enrolled in CureGN, with a target to enroll a minimum of 80% of participants with accessible slides.

Kidney biopsy glass and digital electron microscopy images will be de-identified by a designated CureGN study personnel at the enrolling site. The de-identified pathology materials, labeled with a CureGN biopsy identifier, are sent to a CureGN Scanning Facility. In some cases, the enrolling center may serve as the a Scanning Facility. Upon scanning, all digital pathology materials undergo quality control (QC) for metadata, image quality, and identification masking compliance, and are uploaded in the CureGN Digital Pathology Repository (DPR). The digital renal biopsies that are complete and pass QC are made available to investigators to conduct core and ancillary studies using human and/or computer vision.

3.6. FORMALIN-FIXED AND PARAFFIN EMBEDDED BIOREPOSITORY

A registry of the formalin-fixed and paraffin embedded (FFPE) kidney tissue will be generated. When available, FFPE tissue blocks containing the remaining tissue from patient's clinical biopsy will be collected and stored in the CureGN biorepository for future research. Please see the manual of operating procedures for submission details.

3.7. RETURN OF GENETIC RESULTS

The return of genetic results, inclusive of genetic variants diagnostic for kidney disease and associated with increased risk for kidney disease, as well as secondary findings, as defined as clinically actionable by the American

College of Medical Genetics v3.1., may be offered at no cost to participants who have consented to the collection of their genetic material. If a potential result is found in the course of ongoing research, participants will be contacted by the DCC, their local site, or designated CureGN institution for the purpose of returning results to participants.

Participants will notified by letter or phone call that they potentially have results to share. If the participant would like to receive these results they will be asked to consent to additional testing confirmatory testing, returned results and genetic counseling. This consent can be done electronically or with a wet signature. Participants/their legal guardians may elect to not proceed with the CureGN return of genetic results procedure.

Participants/legal guardians will be remotely counseled about genetic testing, the options of genetic test results they may choose to receive (kidney disease related and/or unrelated) and the process for confirming the genetic results using a commercial Clinical Laboratory Improvement Amendments (CLIA) approved laboratory. Once consented, the participant will need to provide, via a postal delivery service, an updated sample of genetic material to the CLIA-approved laboratory. When genetic results from the CLIA laboratory are available, the participant will then receive a post-result genetic counseling session. The results will be incorporated in the participant's EHR of the site that provided the genetic counseling to the patient.

Additional surveys may be asked of the participant including questions about the Return of Results process. No results will be returned to participants without additional CLIA testing and genetic counseling offered. Participants with data collected as minors will be asked to reconsent into the study but will not be required to do so to receive their results, however they will have to consent to additional CLIA testing and genetic counseling. Minors (under 18 years of age) will provide assent for CLIA-confirmation, if capable. In the case of adolescents (children ages 13-17), they will be invited to assent and participate in both the genetic testing and counseling sessions described above.

3.8. RETENTION

Retention of the CureGN cohort is essential to optimize the scientific value of this consortium. To that end, there are several strategies that will be utilized in this study to maintain the enrolled patient population.

3.8.1. STUDY BURDEN

- Study visit windows are contiguous to provide flexible visit windows,
- Visit frequency adjusts over time to provide additional flexibility
- Remote visits may be conducted by phone, email or in community settings as the patient prefers and clinical center is able,
- In-person visits may be conducted at any point during the year and may be conducted in community settings as the clinical center is able, in order to make it as convenient as possible for the study participant. In-person visits include the collection of biospecimens. If a participant's in-person visit must be conducted at a study site with limited laboratory processing capabilities, the limited biospecimen collection protocol will be followed [see MOP/Biospecimens/Limited Capacity for instructions].

3.8.2. PARTICIPANT ENGAGEMENT

- Two back-up contacts will be requested from every study participant, prioritizing family or friends who are designated as "will always know how to reach the participant." These contacts may be used for study-related contact if the participant becomes unresponsive to study contact and at-risk for becoming lost to follow-up.
- Enhanced patient engagement through study newsletters, greeting cards, and methods for patients to provide direct feedback to the CureGN study leadership through the patient advisory board.

3.9. SAMPLE SIZE AND POWER CALCULATIONS

The statistical power calculations are based on the following assumptions: (1) data will be obtained from more than 66 sites coordinated by the four PCCs; (2) average follow-up of 2 years or 5.5 years; and (3) a loss of 10% of the available follow-up due to participant loss of follow-up, withdrawal, post-enrollment exclusion or death. Additional assumptions include: a power of 80%, a significance level of 0.05, an intra-cluster correlation of 0.05, and a between-facility normalized standard deviation of the sample size of 0.15. Power is computed for a range of outcomes and sample sizes, representing different study questions and subgroup comparisons such as within and between diagnosis groups (FSGS, MCD, MN, IgAN), among pediatric or among adult patients, and comparisons with control populations. Group sizes for time-to-complete remission of proteinuria excluded 1/3 of the group who were in remission at enrollment. The range of event rates for selected clinically-meaningful events (composite of ESKD/death, 50% loss of eGFR from baseline, and complete remission of proteinuria) and standard deviations of lab values (eGFR, urine protein creatinine ratio [UPCR]) were based on published literature and early observed data in the recruited CureGN cohort[24-28]. These rates are not outcome-specific; any analysis of an event with a similar rate on the data described would have the minimum detectable effect sizes indicated in Table D.

Table D: Minimum Detectable Effect Sizes for Different Outcomes by Observation Period, Expected Event Rate, and Cohort Size

Time-to-Event Outcomes (Cox)	**Average Follow Up Time**	**Event rates per person year**	**MDHR* for n=300 (150/group)**	**MDHR* for n=600 (300/group)**	**MDHR* for n=1200 (600/ group)**	**MDHR+ for n=2400 (1200/ group)**
Time to ESKD **or** death	2 years	0.03-0.08	3.9 to >10	2.6 to 8.0	2.0 to 4.1	1.8 to 3.1
	5.5 years		2.2 to 4.6	1.7 to 2.8	1.5 to 2.1	1.4 to 1.9
Time to loss of 50% eGFR **from baseline**	2 years	0.04-0.15	2.4 to >10	1.9 to 4.7	1.6 to 3.1	1.5 to 2.5
	5.5 years		1.8 to 3.4	1.5 to 2.4	1.4 to 1.9	1.3 to 1.7
Time to complete remission of proteinuria (<0.3 g/24hrs)	2 years	0.20-0.70	1.5 to 2.1	1.3 to 1.7	1.3 to 1.5	1.2 to 1.4
	5.5 years		1.4 to 1.7	1.3 to 1.5	1.3 to 1.3	1.2 to 1.3
Slope Outcomes (Linear)		**Slope SD of subgroup**	**MDDS+ for n=300 (150/group)**	**MDDS* for n=600 (300/group)**	**MDDS* for n=1200 (600/group)**	**MDDS* for n=2400 (1200/group)**
eGFR slope (per year)		18.4-26.4	6.0-8.6	4.2-6.1	3.0-4.3	2.1-3.0
Repeated Continuous Outcomes (Mixed Model)	**Average Follow Up Time**	**Lab SD of subgroup**	**MDDS* for n=300 (150/group)**	**MDDS* for n=600 (300/group)**	**MDDS* for n=1200 (600/group)**	**MDDS* for n=2400 (1200/group)**
eGFR	2 years	13.5-22.6	3.94-6.59	2.77-4.64	1.96-3.27	1.38-2.31
	5.5 years		1.68-2.80	1.17-1.96	0.82-1.38	0.58-0.97
UPCR	2 years	2.4-4.5	0.59-1.12	0.42-0.79	0.30-0.56	0.21-0.39
	5.5 years		0.19-0.36	0.14-0.25	0.10-0.18	0.07-0.13
Event Rate Outcomes (Poisson)		**Event rates per**	**MDRR* for n=300**	**MDRR* for n=600**	**MDRR* for n=1200**	**MDRR* for n=2400**

Table D: Minimum Detectable Effect Sizes for Different Outcomes by Observation Period, Expected Event Rate, and Cohort Size						
Time-to-Event Outcomes (Cox)	**Average Follow Up Time**	**Event rates per person year**	**MDHR* for n=300 (150/group)**	**MDHR* for n=600 (300/group)**	**MDHR* for n=1200 (600/ group)**	**MDHR+ for n=2400 (1200/ group)**
		100 person years	**(150/group)**	**(300/group)**	**(600/group)**	**(1200/group)**
Relapse rate		7.6-38.8	0.92-2.04	0.64-1.44	0.45-1.02	0.32-0.72
Remission rate		35.1-72.2	1.95-2.78	1.37-1.96	0.97-1.38	0.68-0.98
*MDHR, minimum detectable hazard ratio; MDDS, minimum detectable difference in slopes; MDRR, minimum detectable rate ratio						

3.10. STATISTICAL ANALYSIS

Descriptive statistics will be used to characterize the overall cohort and subgroups of interest. Summary statistics, including mean (standard deviation), median (interquartile range), and frequencies will be calculated. Graphical methods will be used to examine distributions, identify potential influential points and guide in data transformations as needed. Relationships between variables will be similarly assessed for linearity, symmetry, and homoscedasticity. To compare subgroups within the larger cohort or to other cohorts, we will use standard statistical tests (e.g., t-tests, analysis of variance [ANOVA], Kruskal-Wallis, Mann-Whitney as appropriate). Model-based analyses (generally including other covariates) will include generalized linear models (e.g., linear, logistic or Poisson regression), linear mixed models with center as a random effect to account for within-center similarity, survival analysis methods including both Cox regression (perhaps stratified by other factors, or with repeated events) and parametric (accelerated failure time) models, and penalized regression models to avoid over-fitting. This set of analysis tools is suited for cross-sectional, retrospective and prospective (longitudinal) analyses of multiple outcomes and multiple exposures and/or biomarkers. Comparisons between the Screening Log and enrolled patients will allow assessment of the extent of recruitment and consent bias in the sample.

In addition, we will continue to assess referral bias by comparing the characteristics of patients who live close enough to the center to consider it their location for routine care (local cohort) and patients who were referred to a CureGN center from a greater distance (referral cohort).

Outcome measures for the many possible research aims will include, for example, measures of disease activity (e.g., time to complete remission defined as proteinuria <300mg/day adjusted for body surface area, change in proteinuria, or change in UPCR over time); measures of eGFR change (e.g., time to a fixed eGFR loss, time to a 40% or 50% reduction in eGFR, and eGFR slope); time to ESKD or death; time to cause-specific events (e.g., infection, thrombosis, malignancy); and PRO measures. Changes in continuous outcomes, such as urine protein and eGFR, will be graphically depicted using restricted cubic splines. Semi-parametric models will be constructed to identify distinct subgroups within the population based on clusters of trajectories.

To identify predictors of renal and non-renal outcomes, including therapeutic response, time-to-event and longitudinal analyses will be performed. Cox regression models will be used when analyzing defined time-to-event outcomes and will use left truncation when interest is in time from biopsy to allow each patient's experience to contribute to the appropriate interval since biopsy in the analyses. Analyses of longitudinal exposure factors, e.g., a slope or change of a factor over time, would involve non-intersecting measurement (exposure) periods for the predictor factor and follow-up periods for the outcome in time-to-event analyses. Event rate outcomes will be estimated using recurrent event models, e.g., for repeated remission or relapse events and hospitalizations. Mixed longitudinal regression models will be applied for disease progression measures such as eGFR or UPCR over time. In these longitudinal models, the covariance structure will be modeled either using patient-level random effects or

using a more complex covariance structure if needed. Flexible functional forms for time may be used to model non-linear effects.

Potential predictors may include clinical characteristics, genetic markers, and/or novel biomarkers. For factors likely to be influenced by treatment-by-indication bias, we will evaluate whether techniques such as instrumental variables analysis are appropriate. Special consideration will be applied when analyzing molecular biomarkers. For example, to screen a large number of potential predictors without losing statistical power, analyses will be performed in a hypothesis-generating manner. Regression analysis will be performed to obtain p-values for the associations between an outcome and a biomarker, and the Benjamini-Hochberg method will be used to control false discovery rate to determine a pool of potentially important biomarkers. Selected biomarkers will be analyzed and grouped according to the relevance of their biological functions. Approaches using penalized regression with cross-validation will also be used to explore important covariates without risk of over-fitting.

To identify patient subgroups with shared clinical presentations, outcomes, and response to treatment, we will use unsupervised and supervised machine learning methods. Unsupervised methods, such as cluster analysis, will allow us to explore novel groupings of patients and assess their associations with outcomes. Supervised methods will include penalized regression, random forests, support vector machines, quadratic discriminant analysis, and a SuperLearner for incorporating a large number of variables to predict clinical outcomes. In addition, as computer-aided pathology feature detection becomes available, we will use pre-trained kidney-specific convolutional neural networks to assist pathologists with image processing.

4. HUMAN SUBJECTS

4.1. PROTECTION OF HUMAN SUBJECTS

4.1.1. INSTITUTIONAL REVIEW BOARD

This study and analysis will be performed under single Institutional Review Board (sIRB) oversight. sIRB approval for study of human subjects will be obtained by the DCC prior to initiation of protocol at each enrolling site. sIRB approval is required for sites in the USA. International sites will abide by their local human subjects research review board. Revisions to the study protocol and changes in the study design will also be submitted to sIRB for approval prior to implementation.

Participants will be enrolled in the protocol with informed consent (and informed assent when applicable) which will include the gathering of protected health information (PHI), the collection of blood and urine specimens beyond that normally performed for clinical care, sharing of archived kidney tissue specimens collected for routine clinical care, and the collection of medical and PRO information at defined intervals.

4.1.2. PARTICIPANT CONFIDENTIALITY

Special procedures for ensuring participant confidentiality will be implemented. Data transmission and the distributed data systems have multiple layers of security, as discussed below in Section 6, Study Management. Each study participant will be assigned an identification number. Only this number will be used to identify participants in any individual tabulation. The PHI that is collected will represent the minimum necessary to successfully execute the study.

Personally identifying information, such as participant name and social security number entered into the database at the site level, will only be visible to site study personnel and the Data Coordinating Center (DCC). SSN will only be asked if it is allowed at the site level. Access to computerized data will be restricted to study personnel. Password authorization will be enforced.

Other personal identifiers such as census tract, date of birth, and visit/clinical dates will be collected and accessible to the DCC including cell phone number and email address PCC lead coordinators will also have access to these data elements, for sites within their PCC, for monitoring purposes.

All identifiable information accessible to the DCC will be housed separately from the main CureGN cohort data to maintain the strongest safeguards for patient data protection. Identifiable information will only be accessed for tasks required for performing the study and in line with participant consent.

It is expected that only group data will be published. If individual participant data are to be published, no identifying information will be included. The study files will be maintained in a secure location as described below.

Authorized representatives of the Sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), participating clinical institutions, DCC monitoring staff, as well as the sIRB, may have access to medical records and records from participation in this study as needed to ensure the accuracy of the findings. The DCC monitoring staff may contact participants. For example: to notify them of potentially available research studies and how their research involvement is impacting research.

4.1.3. CERTIFICIATE OF CONFIDENTIALITY

To help protect participant privacy, a Certificate of Confidentiality has been obtained from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify a study participant, even by a court subpoena, in federal, state, or local civil, criminal administrative, legislative or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify a participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded research projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Even with the Certificate of Confidentiality, the investigators continue to have ethical and legal obligations to report child abuse or neglect and to prevent an individual from carrying out threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators will release information to protect the participant or another person.

4.1.4. INFORMED CONSENT

The consent process will follow sIRB guidelines, though may differ somewhat by enrolling sites in accordance with local IRB policy. Participants will be asked to complete all study procedures. However, each study participant is able, during any study visit, to decline one or more of the data collection procedures without withdrawing from the study.

The initial informed consent document will be signed and dated by the participant before initiation of any study-related activity. Electronic consent may be obtained by study participants if requested. Video consent may also be available to participants.

If initial consent is given over the phone the participant will sign informed consent at the first in-person visit.

Before obtaining a potential participant's signature on the informed consent document, the local study investigator or designee will review the details of the consent form orally with the potential participants and answer any questions the participant has concerning involvement in the study. The original signed consent form will be stored at the site, and a copy of the signed consent form will be given/or emailed to the participant.

Participants who reach age 18 years while participating in the study will be reconsented at the time of their next in-person study visit. If a participant reaching the age of majority [18 years] is unable to attend an in-person visit, a re-consent may be completed via telephone, or electronically via email with distribution of the informed consent document, review of the consent with the participant by the study investigator or designee, and

documentation of the consent date, time and consenting study team member(s). If a subject turns 18 but is not able to be reached for reconsent, continuation of the informed consent is assumed, and the study team should continue to follow the subject through chart extraction of data.

Participants returning to the study after a period of Lost to Follow Up will only be required to re-consent if the study consent has changed or the participant has reached the age of majority following the most recent study consent.

4.1.5. RISKS TO THE PARTICIPANT

Participants enrolled in this study will experience more than the normal amount of testing that is customary for their clinical care. Additional time will be required for the gathering of medical and PRO information. Blood and urine will be collected and stored for special tests and archival storage which are not normally required for clinical care. Venipuncture carries risks of pain and bruising at the puncture site. There is also a risk of anxiety, a small risk of dizziness, and/or syncope associated with blood draws.

The remote blood collection device, used for optional blood collection with remote visits, is a non-significant risk device with potential risks of the following:

- Sensation of pressure or suction during use.
- Dizziness, lightheadedness, or fainting at time of collection.
- Minor dermal response such as erythema (redness), edema (swelling), or bruising around sampling site that can last up to several days.
- Temporary sensitivity and/or pain at the sampling site following use.

4.1.6. UNAUTHORIZED DATA RELEASE

There is always the theoretical possibility of unauthorized release of Health Insurance Portability and Accountability Act (HIPAA) PHI about participants. Such disclosure would be extremely unlikely to involve a threat to life, health, or safety but would be a serious invasion of the participant's privacy. It is conceivable that such disclosure could have psychological, social, or legal effects on the participant. The standard security procedures will effectively minimize the risk of unauthorized disclosure of data. All study personnel who have access to participant data will complete their local institutions requirements for **PROTECTION OF HUMAN SUBJECTS** training as required by NIH guidelines. The computer systems on which data are maintained use password protection procedures to prevent access by unauthorized users. Data to be used for analysis will contain only the assigned identification numbers.

4.1.7. ADVERSE EVENT MONITORING

Reporting Responsibility: Only AEs possibly or probably related to this observational study will be recorded.

Events related to the disease or therapy of the participant need not be reported as *Observational Study-Related* AEs. The onset and end dates, severity, and relationship to study procedure(s) will be recorded for each AE. Any action or outcome (e.g., hospitalization, additional therapy, etc.) will also be recorded for each AE. Participants will be questioned and/or examined by the investigator or his/her designee for evidence of AEs.

All AEs and serious AEs (SAEs) reported by the investigator to the CureGN DCC will be reviewed. The DCC may request additional information from sites for analysis of these events. Sites will report SAEs related to the study according to the time frames outlined below.

All events that are serious and related (possibly or probably) to the observational study must be reported to the DCC within 24 hours of the investigator being informed of the event. Follow-up information about a previously reported serious and related AE may be reported to the DCC within 7 working days of the investigator receiving the information; however, important follow-up information must be submitted within 24 hours. All deaths related to a study procedure must be reported to the DCC within 24 hours of the investigator being informed of the event.

Definition of Adverse Event: An adverse event (AE) is any untoward medical occurrence or unfavorable and unintended sign in a research participant that occurs during or as a result of a research procedure. For this study, the majority of the procedures are standard clinical care, and adverse effects of clinical care will be tracked as complications but will not be considered adverse study events. Each center will review the list of study procedures and identify the specific procedures that are not standard-of-care at their institution, and these will be considered research procedures. Complications that are a result of research procedures will be reported and tracked as AEs.

Assessment of Event Severity and Relationship to Study Procedure/Treatment: The modified World Health Organization (WHO) grading system will be used for grading severity of AEs (See Manual of Procedures). For AEs not covered by the modified WHO grading system, the following definitions will be used:

Mild:	Awareness of sign, symptom, or event, but easily tolerated
Moderate:	Discomfort enough to cause interference with usual activity, and may warrant intervention
Severe:	Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention
Life-threatening:	Immediate risk of death

The investigator must also assess the relationship of any AE to the research procedure, based on available information, using the following guidelines:

Unlikely related:	No temporal association, or the cause of the event has been identified; or the procedure cannot be implicated. AEs that are unlikely related are not reportable in this observational study.
Possibly related:	Temporal association, but other etiologies are likely to be the cause; however, involvement of the procedure cannot be excluded
Probably related:	Temporal association; other etiologies are possible, but unlikely

Definition of Serious Adverse Events: A serious AE (SAE) is any adverse experience that results in any of the following outcomes:

- Death;
- Life-threatening AE (i.e., one that places the participant, in the view of the investigator, at immediate risk of death from the AE as it occurs);
- Persistent or significant disability/incapacity;
- Required in-patient hospitalization, or prolonged hospitalization;
- Congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, if based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.1.8. BENEFITS TO THE PARTICIPANT

There are no direct benefits to participants for participation in the study. Potential benefits include the satisfaction of altruism and detection of new information that may improve the management of patients with glomerular diseases in the future.

4.2. SPECIAL POPULATIONS

4.2.1. INCLUSION OF WOMEN

This is a multi-center study drawing on a clinical population from enrolling sites in the United States, Canada, and Europe. Women will be recruited into the study. It is envisioned that the representation of women will correspond to the fraction of women in the population diagnosed with biopsy confirmed primary glomerular diseases emanating from FSGS, MCD, IgAN, and MN. Special efforts will be incorporated into the recruitment process to facilitate the optimal inclusion of women with these diseases in the study.

4.2.2. INCLUSION OF MINORITIES

Racial and ethnic minority groups will be recruited into the study. It is envisioned that the representation of persons comprising racial and ethnic minority groups will correspond to the fraction of those groups in the population diagnosed with biopsy confirmed primary glomerular diseases emanating from FSGS, MCD, IgAN, and MN. Special efforts will be incorporated into the recruitment process to facilitate the optimal inclusion of persons of racial and ethnic minority groups. Recruitment will be monitored to ensure adequate representation of minority groups.

4.2.3. INCLUSION OF CHILDREN

Children will be recruited into the study. It is envisioned that the representation of children will correspond to the fraction of children in the population diagnosed with biopsy confirmed primary glomerular diseases emanating from FSGS, MCD, IgAN, and MN. Special efforts will be incorporated into the recruitment process to facilitate the optimal inclusion of pediatric cases in the study.

4.3. OBSERVATIONAL STUDY DATA SAFETY AND MONITORING PLAN

Accepted principles of data and safety monitoring will be observed throughout the conduct of the CureGN study. The NIH will appoint an independent Observational Study Monitoring Board (OSMB) that will provide study oversight. The OSMB will approve the study protocol prior to enrollment and will also approve all subsequent protocol revisions.

Each PCC principal investigator in partnership with the DCC will be responsible for monitoring the enrollment of participants and submission of high-quality data to the DCC. The DCC will be responsible for monitoring for effective conduct of the protocol and accurate and timely data submission.

Study training materials will be generated and used across the consortium for training of study personnel.
Data will be routinely exported from the data management system, examined for accuracy and completeness, and backed up to secure storage devices. The process of data cleaning, queries, and correction will be ongoing throughout the study. A technical report detailing specific project methodology, response rates, and other details will be produced at the conclusion of the study.

5. STUDY ORGANIZATION

5.1. PARTICIPATING CLINICAL CENTERS (PCC)

The PCCs will have primary responsibility for participant enrollment, maintaining acceptably high rates of follow-up and data collection, obtaining data of high quality, and interpreting, presenting, and publishing findings from the study. Four PCCs serve as clinical center hubs, with additional clinical sites responsible for study participant enrollment, retention, and protocol implementation under the guidance of the respective PCC and overall CureGN consortium leadership.

5.2. DATA COORDINATING CENTER (DCC)

The DCC is located at the University of Michigan Health System in Ann Arbor, Michigan. The DCC contributes content area expertise and shares in scientific leadership of CureGN. The DCC has developed a communication infrastructure that includes meetings, teleconferences, electronic mail and bulletins, interactive web-based encounters, and written correspondence. The DCC assists in preparation of scientific publications. The DCC has the major responsibility of creating and maintaining the study database and data collection systems for CureGN, ongoing evaluation of data quality and performance monitoring of the PCCs, and statistical analyses of the data. The DCC also maintains a comprehensive Manual of Procedures that will govern the conduct of the study. The DCC will partner and/or contract with other institutions to execute its responsibilities.

5.3. STEERING COMMITTEE

The primary governing body of the study is the Steering Committee, which includes each of the Principal Investigators of the PCCs, the Principal Investigators of the DCC, a Chairperson appointed by the NIDDK, and the NIDDK Project Officers. Each PCC, the DCC, the NIDDK, and the Steering Committee chair has one vote for decisions brought to the Steering Committee. The Steering Committee is charged to develop, approve, and update the study protocol as needed, and to develop policies for the study pertaining to access to participant data and specimens, ancillary studies, performance standards, and publications and presentations. The Steering Committee meets to discuss study progress and to resolve problems arising during study conduct. The Steering Committee may establish subcommittees to further develop or manage specific components of the study, such as ancillary studies or publications. Working groups may also be established, e.g., to prepare manuscripts, presentations and assist in the work of the consortium.

6. STUDY MANAGEMENT

6.1. DATA COLLECTION, DATA COLLECTION FORMS, AND DATA ENTRY

The DCC will utilize *REDCap* as the data management nucleus for the CureGN studies. *REDCap* is a secure web application for building and managing online surveys and databases.

The DCC will utilize *REDCap* to create electronic case report forms to capture all relevant study data for the core study and all investigational/research protocols that are developed and implemented during the course of the study. The *REDCap* system allows real-time monitoring of study data for protocol adherence, quality assurance, AE reporting, discrepancy reporting, and other trends.

6.2. DATA MANAGEMENT

Study data will be entered into the electronic data entry system by study coordinators at each study site. These data will be encrypted and transferred to the DCC and stored on a secure virtual server maintained by the Data Management and Coordinating Center of the Rare Diseases Clinical Research Network (RDCRN), based at Cincinnati Children's Hospital Medical Center and funded by NCATS. Access to the server and data entry system is limited and requires a unique institutional username and password combination, as well as multi-factor authentication through Duo. The servers are backed up frequently and physically stored in AWS region US-East-1 (N. Virginia). All analysis of the data sets will utilize de-identified or coded data sets. Transfer of batch data from site-specific databases or other electronic data sources will be assessed individually for each clinical site based on feasibility and data quality.

6.3. QUALITY CONTROL AND DATABASE MANAGEMENT

The first steps in ensuring protocol compliance are good protocol design and careful orientation of study personnel. Prior to study initiation at any of the PCCs, the DCC will organize training for study coordinators and data entry personnel.

The electronic data entry system has built-in data checks as part of study quality assurance. The data analysts and clinical monitor will produce reports from the database to look for inconsistencies in submitted data, particularly for repeated measures data elements, even if data do not fall outside of built-in validation routines. Studies of intra-

subject and inter-subject data variability by PCC as well as intra-center and inter-center data variability will be used to further ascertain random or systematic data quality issues.

Protocol compliance will be assessed by monitoring the submission of data at required intervals. Data inconsistencies and discrepancy reports will be reviewed by the data analysts and the clinical monitors so that necessary queries can be generated and sent to the PCC study sites for verification and resolution. In addition, the clinical monitor will perform a remote monitoring visit for each PCC at least once a year to review compliance with overall study goals and data quality metrics, regulatory compliance, and assess protocol adherence. These visits will include PCC leadership, NIDDK, and the DCC.

The lead PCC coordinator will be responsible for monitoring data quality and data entry timeliness at their sub-sites. Periodic requests may be generated for the submission of random source documents to assess the quality of data acquisition and data entry at each site.

6.4. DATA SECURITY AND DATA TRANSFER

Personnel at each study center will collect and enter data into the web-based data entry system. The following data security contingencies are in place:

- Compliance with Industry Standards Regarding Data Security (HIPAA)
- Audit trails are maintained for all activity and all changes to any data element
- All servers, web servers, firewalls, etc. are configured and maintained according to industry best practice guidelines for backup, security, continuity of operations, and protection of PHI
- All data are available only to authorized users from each site after secure login with encryption, with all site activity audited at the user level
- All transmissions between the Internet and the database are encrypted using at least 128-bit encryption algorithm
- There is a comprehensive security plan in place

Detailed instructions on the use of the database platform, data element definitions, and a code list will be provided in a Manual of Procedures. Each study site will be provided a copy of this manual, and the entire manual will be available on the study web site, and in the Help area of the database user interface.

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