CureGN: Cure Glomerulonephropathy Network

Core Study Protocol

Version 2.0

January 29, 2020

Sponsor:
NIH-NIDDK
NephCure Kidney International

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Protocol: CureGN Protocol 2.0: Cure Glomerulonephropathy Network	Version/Date: 1.1/July 28, 2014 1.2/ September 8, 2014 1.3/June 25, 2018 2.0/November 12, 2019
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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 DCC CureGN_Regulatory@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
DCC	Data Coordinating Center
DPR	Digital Pathology Repository
eGFR	Estimated glomerular filtration rate
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
SMS	Short message service
UPCR	Urinary protein: creatinine ratio
WHO	World Health Organization

1. 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, produce 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?

2. BACKGROUND/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 ESKD. 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]. Bovine serum albumin targeted antibodies have been identified in childhood onset MN[13]. 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[14-18]. 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[19].

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[20, 21], with some currently under prospective evaluation as prognostic and predictive biomarkers[22]. 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[20]
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.

3. AIMS

3.1. CUREGN CONSORTIUM AIMS

Aim 1: Maintain and support the infrastructure for the CureGN Consortium and its ancillary study program to perform patient-relevant research

- **Aim 1a:** Implement efficient study administration procedures to accomplish the consortium goals
- **Aim 1b:** Engage patients as partners in research
- **Aim 1c:** Engage junior investigators

Aim 2: Conduct a prospective cohort study of children and adults with MCD, FSGS, MN, and IgAN

- **Aim 2a:** Recruit and retain a diverse population of children and adults into CureGN
- **Aim 2b**: Assure high-quality data and biosamples collection, including DNA and RNA
- **Aim 2c:** Obtain accurate renal, non-renal, and patient-reported outcomes

Aim 3: Promote pilot and ancillary studies that will foster high-quality, multi-disciplinary investigations, including collaborations outside the CureGN network and supported by innovative public-private partnerships

Aim 4: Integrate multiple CureGN data domains to uncover novel disease features and delineate pathophysiologic pathways for more precise disease characterization, diagnosis, prognosis, and treatment strategies.

3.2. 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.

4. INVESTIGATION PLAN

4.1. STUDY METHODS

4.1.1 Overview

The CureGN study is a multi-center prospective cohort study of approximately 2,400 active adult and pediatric (<18 years of age) patients with biopsy-documented IgAN, FSGS, MN, and MCD. For each disease category, approximately 600 participants will be recruited and retained. Participants will be recruited concurrently from each of the four Participating Clinical Center (PCC) networks: Columbia University, Midwest Pediatric Nephrology 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 enrollment criteria below will be enrolled if they or their legally authorized representative(s) provide signed informed consent. 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, until recruitment goals are met for each disease category and to account for attrition.

4.2. PARTICIPANT SELECTION

4.2.1 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

4.2.2 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

4.3. SCHEDULE OF VISITS, TEST, AND ASSESSMENTS

4.3.1 Visit Schedule

Table A provides a schematic of the visit schedule. The first visit that a participant has after consenting to CureGN 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 each year. Starting in the fourth 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 Text messaging details can be found in section 4.3.5.

Table A: Visit Schedule										
Visit Type	Enrollment V0	Year 1		Year 2		Year 3		Years 4+		
In Person	X	X		X		X		X		
Remote		X	X	X	X	X	X	X		
Relapse* (optional)		X		X		X		X		
Text Message	Monthly									
*May occur in place of a regularly scheduled visit										

4.3.2 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. If informed consent is obtained prior to V0, the subject should be instructed to collect a 24 hour urine to bring to the enrollment visit (V0).

4.3.3 Enrollment Visit (V0)

4.3.3.1. Consent

Prior to any research related procedures being performed, comprehensive informed consent, and if applicable, assent 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.

4.3.3.2. Data Collection

At V0, clinical data will be gathered by participant interview, participant questionnaire, and chart extraction as outlined in Table B (Data Elements). This includes medical history, prior disease course, medication exposures, and local laboratory results. 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 healthcare providers.

A brief, focused physical exam will be performed, and PRO measures will be completed. Biospecimen collection will occur, as per Table B (Data Elements) and Table C (Biospecimen Volumes). A spot urine collection will be obtained. If the participant consented prior to V0, a 24-hour urine sample should be collected (or first morning urine from participants unable to collect a timed 24 hour urine) prior to the in-person visit. For participants who are unable to collect a 24-hour or first morning void, random urine sample will be collected during the visit.

4.3.3.3 SMS Preparation

Introduction to the SMS patient reported data collection procedures will be conducted, patient/guardian preferred cell phone number will be collected and entered into the database to initiate this system. Patient preference for day of the week/time of day for text receipt and text language will be entered to the database. Vacation or other text hold/discontinuation request procedures will be reviewed and provided to the participant for future use.

Participants may opt out of SMS data collection procedures. This will be noted in the study consent form and in the SMS CRF.

4.3.3.4 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 may be withdrawn from the study if biopsy review by the CureGN study pathologists 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 by: review of the subject's de-identified, uploaded biopsy report. Glass slides and electron microscopy images, may be requested if the biopsy report is unclear or for supplemental review at the pathologist's discretion.

4.3.3.5 Digital Pathology Repository

De-identified biopsy slides will be scanned into the CureGN Digital Pathology Repository for pathology scoring and future research for all consented participants for whom slides are available. Pathology slide scanning may occur at the local pathology site or at the CureGN Image Coordinating Center. Participants for whom slides are not available may be enrolled in CureGN, with a target to enroll a minimum of 80% of participants with accessible slides.

4.3.4 Follow Up Visits

4.3.4.1 In-Person Visits

Each participant will have one in-person visit every year of the study. At this visit there will be data collection, as outlined in Table B, a brief focused physical exam, PRO measures, and biospecimen collection. In addition to a spot urine collection, participants who are able should collect a 24-hour urine sample (preferred) or first morning void prior to the visit. Chart abstraction should be conducted to complete clinical data collection.

4.3.4.2 Waiver for Annual In-Person Visits

In rare circumstances, after notifying the PCC, participants may be transitioned to remote only follow up visits. Typical scenarios for this include: subjects who decline in-person follow up, subjects moving to location with no active CureGN site, subjects transitioning to adult care at a non-CureGN site and unable to return for annual in person visits. Participants who are able should be encouraged to return to the standard in-person schedule whenever possible.

4.3.4.3 Remote Visits

All study participants will have two remote visits in each year of their first three years of participation in CureGN, and one remote visit per year starting in their fourth year of

participation. Remote visits will maintain connection with the participant, ascertain major clinical events (e.g., interval ESKD, hospitalizations, relapse, and major medication changes, etc.), collect PRO data and assure that a study visit is scheduled at least annually. Remote visits may be conducted by phone, email, text, or other means. PRO measures may be completed via secure email link or using a mailed and returned paper version, per participant preference.

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.

4.3.4.4 Follow Up After Onset of ESKD

Following onset of 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 take place in lieu of the regularly scheduled 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, dates 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.

4.3.5 SMS Data Collection

Text messages will be sent on a monthly basis to all CureGN participants to ascertain participant reported information about edema, visible hematuria, proteinuria, kidney medication adherence, and major remission, relapse or renal replacement therapy events.

4.3.6 Patient Reported Information (PRI) Data

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

Self-report measures will be used for adults and children age 8 years and older. Parent/guardian-proxies will complete the measures for participants age 0-9 years of age.

Patient reported outcome measures include novel PRO measures for patients with kidney proteinuric disease, items from the Patient Reported Outcomes Measurement Information System [PROMIS}, and the most troublesome symptom question. In addition, the PedsQL version 4 generic measure [15 items] will be completed by children age 8-17 for one year. Redundancy in

the questions is present to assist with the study objective to validate disease specific PROs. [See Manual of Procedures for PRO Questionnaire forms

The Morisky Adherence Questionnaire will be completed by participants age 8 and above and parent proxies of participants ages 0 through 9 years. Translated versions will be available for use in English, Spanish, French, Italian, and Polish.

4.4 DATA ELEMENTS

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

Table B: Overview of Data Elements				
Visit	**Enrollment (V0)**	**In-Person Visits[1]**	**Remote Visits**	**SMS Collection**
Census Data				
Demographics	X			
Census Tract	X			
Biopsy diagnosis/Pathology report	X			
Exclusion criteria	X			
Consent/assent	X			
Medical Data				
Comorbidities	X	X	X	
Family history	X	X		
Birth history	X			
Pregnancy history	X	X		
Prior disease course	X			
Interim disease course		X	X	X
Medications	X	X	X	X
Hospitalizations	X	X	X	
ESKD status		X	X	X
Vital status		X	X	
Physical exam	X	X		
Vital signs	X	X		
PRI Data				
PRO questionnaire[2]	X	X	x	
Medication Adherence [Morisky-4][3]	X	X	X	
Local Laboratory Test Results[4]				
Blood chemistries	X	X	X	
Coagulation studies	X	X	X	
Hematology studies	X	X	X	
Rheumatologic serology	X			
Infectious serology	X			
Urine studies	X	X	X	

Biospecimens				
Blood sample collection	X	X[5]		
DNA and RNA collection[6]	X			
Spot urine sample	X	X		
24-hour urine (preferred) or first morning void[7]	X	X		
Pathology slides	X			

1.These include in-person Relapse visits

2-3. See Manual of Procedures for PRO and Medication Adherence measures

4As available in the medical record

5. 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

6. If DNA/RNA is not collected at enrollment it should be collected at the next in-person visit

7If a participant is not able to collect a 24-hour urine or first morning urine, a random urine sample will be collected at the visit

4.4.2 Linkage

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, and census tract to collect residential census tract location at enrollment

4.5 DIGITAL PATHOLOGY REPOSITORY

The pathology materials, including all stained glass slides, EM images, and pathology report, are de-identified by designated CureGN study personnel at the enrolling site. The de-identified pathology materials, labeled with a CureGN subject identifier, are sent to the CureGN Image Coordinating Center, where the glass slides are scanned into whole slide images. In some cases, scanning may occur at the enrolling center. Upon scanning, all pathology materials are uploaded in the CureGN Digital Pathology Repository (DPR) and undergo quality control (QC) for metadata, image quality, and identification masking compliance. The digital renal biopsies that are complete and pass QC are made available to investigators for morphologic and morphometric analysis by visual assessment and artificial intelligence applications.

4.6 BIOSPECIMENS

Total blood and urine volumes at baseline and follow-up visits are listed in Table C below. Pediatric participants' blood volumes are based on weight at the time of visit.

Table C: Biospecimen Volumes				
	Total Blood Volume (ml)		**Total Urine Volume (ml)**	
Visit type	Enrollment (V0)	In Person Follow Up Visits	Enrollment (V0)	In Person Follow Up Visits
Pediatric participants				
<21 pounds	21	15	80	20
21-<52 pounds	46	15	80	20

≥52 pounds	48	30	80	20
Adult participants	50	30	80	20
Limited Lab Capacity[1]	10	10	10	20

1To be used only for community based in-person visits where laboratory processing is not available. See MOP for directions.

4.7 RETENTION

Retention of the CureGN cohort is essential to obtain 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.

4.7.1 Study Burden:

- Study visit windows are contiguous to provide flexible visit windows,
- Visit frequency adjusts over time so that participants will be required to have one in-person visit and two remote visits per year for the first three years, and then one in-person and one remote visit in the subsequent years, reducing participant burden while maintaining scientific integrity,
- Remote visits may be conducted by phone, email or in community settings as the patient prefers and clinical center is able,
- In-person visit 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.
- Text messages (SMS) will be used to collect a limited set of information from participants on a monthly basis.

4.7.2 Participant Engagement:

- Participants will have access to a personalized CureGN dashboard which will display their SMS data, as well as select other clinical variables collected through the study. The dashboard will also provide an electronic copy of study news items.
- 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.

4.8 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[30-34]. 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						
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		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						

4.9 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.

5 HUMAN SUBJECTS

5.1 PROTECTION OF HUMAN SUBJECTS

5.1.1 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.

5.1.2 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 7, 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. The information is encrypted at the site level. Site personnel have the decryption key, and it is not available to the DCC. 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 for the participants or participant's guardians who consent to text message patient reported information submission by SMS and study patient reported outcome questionnaire completion and/or web-based personalized dashboard for link distribution via email. PCC lead coordinators will also have access to these data elements, for sites within their PCC, for monitoring purposes. 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.

5.1.3 Certificate 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.

5.1.4 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.

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

Before obtaining a potential participant's signature on the informed consent document, the local study investigator or his/her 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 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 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 remotely and 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.

5.1.5 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.

5.1.6 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.

5.1.7 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.

5.1.8 Benefits to the Participants

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.

5.2 SPECIAL POPULATIONS

5.2.1 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.

5.2.2 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.

5.2.3 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.

5.3 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.

6 STUDY ORGANIZATION

6.1 PARTICIPATING CLINICAL CENTERS

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.

6.2 DATA COORDINATING CENTER

The DCC is located at the University of Michigan Health System and Arbor Research Collaborative for Health, both located 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.

6.3 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.

7 STUDY MANAGEMENT

7.1 DATA COLLECTION, DATA COLLECTION FORMS, AND DATA ENTRY

The DCC will utilize the web-based *CureGNLink* as the data management nucleus for the CureGN studies. *CureGNLink* is a database platform developed by Arbor Research Collaborative for Health.

The DCC will utilize *CureGNLink* 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 *CureGNLink* system allows real-time monitoring of study data for protocol adherence, quality assurance, AE reporting, discrepancy reporting, and other trends.

7.2 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 server at Arbor Research Collaborative for Health and the University of Michigan. Access to the server and data entry system is limited and requires a unique username and password combination. The servers are backed up daily and physically stored in a locked facility. 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.

7.3 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.

7.4 DATA SECURITY/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 and 21 CFR Part 11)
- 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 a 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.

7.5 SHORT MESSAGE SERVICE (SMS) AND DASHBOARD DATA MANAGEMENT AND SECURITY

SMS messaging is facilitated by Twilio, a cloud communications platform as a service company that provides a platform to send and receive text messages. Twilio will be used to build an SMS application that initiates and accepts text message interactions for this study. Per data received through an application programming interface with Arbor Research, the platform will initiate the SMS interaction structure and message content for the participant. The platform will initiate the assessment, one question at a time. The SMS system will record a confirmation that the message was sent to the participant. When a participant sends a response to the SMS system, the SMS system will continue with the interaction until the assessment is complete.

The SMS platform consists of software development tools that have been installed on secure, HIPAA compliant servers at the University of Michigan Information Technology & Services (ITS) unit in Ann Arbor, Michigan. These secure servers are managed by ITS.

Twilio utilizes AWS data centers for all production systems and customer data. It performs regular backups using Amazon S3 cloud storage. Once data are transmitted via SMS from the participant, they will be stored on both (1) ITS servers at the University of Michigan and also (2) routed through the University of Michigan to Arbor Research.

Data transmitted to the server will use a website that will be protected by a Secure Sockets Layer certificate, ensuring that all data transmission between a user's browser and the web server are

encrypted. Additionally, all servers will be placed on a private network which can only be accessed by Virtual Private Network. The program website is separate from any electronic medical records or other data storage devices, and there will be no access to other patient-level PHI via the website or server.

The website will be used only to store necessary data to initiate the SMS to the patient. Information stored in the website's database will be limited to participants' study ID, year of birth, telephone number, schedule for message sending and message content which will be entered through a web interface by study personnel only. All data files will be completely backed up in continuous 30 minute intervals to a replicated off-site Disaster Recovery location.

Data stored at the University of Michigan will be collated into reports for the patient-facing website. The patient-facing SMS dashboard for patient self-management will be developed as a login-based website and associated data will be stored on University of Michigan ITS managed servers and accessible only to those who are authorized. Upon logging into the SMS dashboard, a participant will view a summary of their SMS interactions and a limited summary of other clinical data collected in CureGNLink. All data on the dashboard is specific to an individual participant.

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