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Chapter 1

Protocol Summary and Study Contacts

STUDY OBJECTIVE

To determine whether lowering serum uric acid by means of oral allopurinol is effective in preventing or slowing decline of renal function in T1D patients with microalbuminuria or moderate macroalbuminuria who still have only mildly or moderately impaired kidney function.

1.1. PROTOCOL SUMMARY

Study Title	PERL – Preventing Early Renal Loss in T1D: A multicenter clinical trial of allopurinol to prevent GFR loss in type 1 diabetes
Study Phase	Phase 3
Objectives	To determine whether lowering serum uric acid by means of allopurinol early in the course of kidney disease may be effective in preventing or slowing the decline of renal function in T1D patients.
Study Design	Multicenter, double-blind, placebo-controlled, parallel-group randomized clinical trial.
Participating Centers	Joslin Diabetes Center (Boston), University of Minnesota (Minneapolis), University of Colorado (Denver), University of Michigan (Ann Arbor), University of Toronto (Toronto), Northwestern University (Chicago), Albert Einstein College of Medicine (New York), Steno Diabetes Center (Copenhagen, Denmark), Washington University (St. Louis), University of Calgary (Calgary Alberta Canada), Alberta Diabetes Institute (Edmonton, Alberta Canada), Emory University (Atlanta), University of Washington Medical Center (Seattle), University of Texas Southwestern Medical Center (Dallas), Providence Medical Research (Spokane), BC Diabetes (Vancouver)
Subject Population	480 T1D subjects. <u>Inclusion criteria:</u> 1) Male or female T1D patients. 2) T1D continuously treated with insulin within one year from diagnosis. If the onset was after age 35, the presence of one or more of the following will also be required: <ul style="list-style-type: none">• documentation of the presence of circulating T1D-associated autoantibodies at diagnosis or at any other time• history of hospitalization for DKA• plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl). 3) Duration of T1D ≥ 8 years. 4) Age 18-70 years. 5) History or presence of microalbuminuria or moderate macroalbuminuria, or evidence of declining kidney function regardless of history or presence of albuminuria and/or RAS Blocker treatment. Micro-

or moderate macroalbuminuria will be defined as at least two out of three consecutive urinary albumin excretion rates [AERs] or albumin creatinine ratios [ACRs] taken at any time during the two years before screening or at screening in the 30-5000 mg/24 hr (20-3333 µg/min) or 30-5000 mg/g range, respectively, if **not** on RASB agents, or in the 18-5000 mg/24 hr (12-3333 µg/min) or 18-5000 mg/g range, respectively, if **on** RASB agents); Evidence of declining kidney function will be defined as an eGFR (CKD-EPI) decline ≥ 3.0 ml/min/1.73 m²/year, estimated from the slope derived from all the available serum creatinine measurements (including the one at screening assessment) from the previous 3 years. If at least 3 serum creatinine measures are not available in the previous 3 years, then the slope can be derived from creatinine values from the previous 5 years.

6) Estimated GFR (eGFR) based on serum creatinine between 40 and 99.9 ml/min/1.73 m² at screening. The upper and the lower limits should be decreased by 1 ml/min/1.73 m² for each year over age 60 (with a lower limit of 35ml/min/1.73m²) and by 10ml/min/1.73 m² for strict vegans.

7) Serum UA (UA) ≥ 4.5 mg/dl at screening.

8) Valid baseline (Visit 4) iGFR measurement prior to randomization

OR

9) Being an active participant in the PERL Pilot Study.

Exclusion criteria:

1) History of gout requiring allopurinol therapy or xanthinuria or other indications for uric acid lowering therapy such as cancer chemotherapy or extremely high uric acid values (>12 mg/dl).

2) Recurrent renal calculi (history of more than one episode).

3) Use of urate-lowering agents within 2 months before screening.

4) Current use of azathioprine, 6-mercaptopurine, didanosine, warfarin, tamoxifen, amoxicillin/ampicillin, or other drugs interacting with allopurinol. (Refer to 5.3 of the Protocol for Prohibited Medications and Restrictions).

5) Known allergy to xanthine-oxidase inhibitors or iodine containing substances.

6) HLA B*58:01 positivity indicating an increased risk of Stevens-Johnson syndrome in response to allopurinol. (tested before randomization).

7) Renal transplant. Note: All patients with solid organ transplant, corneal transplant (if on cyclosporine or tacrolimus), or bone marrow transplant should be excluded. The current protocol version (v.8) only exclude renal transplants, but there are plans to extend the exclusion to all types of transplant with the next amendment.

8) Non-diabetic kidney disease as indicated by medical history and/or laboratory findings.

9) SBP>160 or DBP >100 mmHg at screening(V1) or SBP>150 or DBP>95 mmHg at the end of the run-in period (V4,4a).

(See Section 3.2 for clarification on rescreen guidelines).

10) Cancer treatment (excluding non-melanoma skin cancer treated by excision) within two years before screening.

11) History of clinically significant hepatic disease including hepatitis B or C and/or persistently elevated serum liver enzymes at screening and/or history of HBV/HCV positivity.

12) History of acquired immune deficiency syndrome or human immunodeficiency virus (HIV) infection.

13) Hemoglobin concentration <11 g/dL (males), <10 g/dL (females) at screening.

14) Platelet count <100,000/mm³ at screening.

15) History of alcohol or drug abuse or history of treatment for these conditions in the past 6 months.

16) Blood donation in the 3 months before screening. (subjects become eligible once 3 months have elapsed since the last donation).

17) Breastfeeding or pregnancy or unwillingness to be on contraception throughout the trial.

18) Poor mental function or any other reason to expect patient difficulty in complying with the requirements of the study.

19) Serious pre-existing medical problems other than diabetes, e.g. congestive heart failure, pulmonary insufficiency.

Study Duration

9-week run-in period, during which RAS (Renin Angiotensin System) inhibition will be introduced and/or standardized, if indicated and BP normalized, if elevated above 140/90 mmHg, followed by a 3-year treatment period and then by a 2-month wash-out period.

Study Treatment, Dosage, and Route of Administration

After the run-in period, eligible subjects will be randomized in a 1 to 1 ratio to receive placebo or oral allopurinol at a dose of 100 mg per day for 4 weeks and then at a dose ranging from 200 to 400 mg per day depending on kidney function.

Efficacy Assessments

Primary outcome measure: GFR (glomerular filtration rate) at the end of the 2-month wash-out period following the 3-year treatment period, measured by the plasma clearance of non-radioactive iothexol (iGFR) and adjusted for the iGFR at baseline.

Secondary outcome measures:

1) iGFR the end of the 3-yr treatment period (before the washout period) adjusted for the iGFR at baseline.

2) iGFR time trajectory estimated from periodical iGFR measurements.

3) eGFR at 4 months estimated from serum creatinine and cystatin C and adjusted for the eGFR at baseline.

4) eGFR time trajectory estimated from quarterly serum creatinine and cystatin C measurements (eGFR).

5) Time to serum creatinine doubling or end stage renal disease (ESRD).

6) AER at the end of the 2-month wash-out following the 3-yr treatment period, adjusted for the AER at baseline.

7) AER at the end of the 3-yr treatment period, adjusted for the AER at baseline.

	8) Time to fatal or non-fatal cardiovascular events.
Safety Assessment	Examination for skin rash, measurements of liver enzymes, serum creatinine, and CBC, carried out 1 month after randomization and every 3-4 months thereafter.
Statistical Methods	Data will be analyzed according to an intention-to-treat approach. Differences between treatment arms in the primary outcome will be tested for significance by means of a linear model with correlated errors. Intervention effects on other secondary outcomes will be tested by mixed-effect models (GFR time trajectory), ANCOVA (AER), and survival analysis (time to serum creatinine doubling/ESRD and CVD events).
Date of protocol	August 16, 2016

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ABBREVIATIONS

AE: Adverse Event

ACE: Angiotensin Converting Enzyme

ACR: Albumin Creatinine Ratio

AER: Albumin Excretion Rate

ALT: Alanine Transaminase

ARB: Angiotensin Receptor Blocker

CBC: Complete Blood Count

CBL: Central Biochemistry Lab

CKD: Chronic Kidney Disease

CRF: Case Report Form

CVD: Cardiovascular Disease

DMC: Drug Monitoring Committee

DBP: Diastolic Blood Pressure

DCC: Data Coordinating Center

DN: Diabetic Nephropathy

DSMB: Data and Safety Monitoring Board

ESRD: End Stage Renal Disease

GFR: Glomerular Filtration Rate

HbA1c: Glycated Hemoglobin A1C

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

IRB: Institutional Review Board

ITT: Intention to Treat

MAP: Mean Arterial Pressure

MOO: Manual of Operations

NO: Nitric Oxide

PCP: Primary Care Physician

PERL: Preventing Early Renal Function Loss in Diabetes Consortium

RAS: Renin Angiotensin System

RASB: Renin Angiotensin System Blocker

SAE: Severe Adverse Event

SBP: Systolic Blood Pressure

SC: Steering Committee

SOP: Standard Operating Procedure

TC: Trial Coordinator

T1D: Type 1 Diabetes

UA: Uric Acid

Chapter 2

Recruitment and Pre-Screening

2.1. Recruitment and Pre-Screening

Potential participants will be sought (1) from among the patients attending the study centers (including satellite centers) involved in the study; (2) by placing advertisements at other health care facilities and in newspapers or other media; (3) by soliciting referrals from other health care providers; 4) by advertising in social media such as GLU, Facebook and Twitter in order to reach patients across the USA, Canada, and Denmark; 5) through the PERL website.

At each clinical site, potential candidates will be identified and contacted according to the procedures established by the local IRBs in compliance with local laws protecting patient confidentiality. Invitation letters to patients attending the study centers will clearly offer the possibility to opt out of any further contacts with the study. Written consent will be obtained from all patients undergoing the screening visit after explaining again the purpose and procedures of the study. In the initial contact and again at the time of the screening visit, study patients will be encouraged to ask questions and they will be reassured that they may withdraw from the study at any time. Written consent will be obtained again at V2 if the consent at V1 was only for the screening procedures. The consent form will again be reviewed and consent affirmed at the visit prior to randomization (Visit 4).

NOTE: For categorization purposes, prospective study participants are called “patients” prior to consent and “participants” after the consent has been signed.

2.2. Patient Recruitment

Recruitment methods may include, but are not limited to:

2.2.1 Review of medical records

A list of all patients with type 1 diabetes (T1D) in the 18-70 age range who were seen in the clinic at least once in the previous 2-5 years is obtained from the Medical Records Department at the site after a HIPAA waiver is granted from the institution's IRB. The patient's record is reviewed for the following:

- Date of birth
- Date of type 1 diabetes diagnosis (duration \geq 8 years)
- Continuous treatment with Insulin within one year of diagnosis
- Serum Creatinine values reported in the past 2-5 years
- Urinary Albumin Creatinine Ratios (ACR) and or Albumin Excretion Rates (AER)'s reported in the past two years
- Most recent Serum Uric Acid results (if available)

Patients that appear to meet the age criteria*, age of onset and duration of T1D, eGFR at baseline, urinary albumin (AER/ACR) or evidence of declining kidney function (eGFR slope criteria), are sent an invitation letter (See Appendix A). After patients have had a sufficient amount of time to opt out of further contact, they should be contacted by phone (in approximately 2 weeks) or at the next visit to the clinic to see if they are interested in participating in the study.

***NOTE:** If diabetes onset was after age 35, the presence of one or more of the following will also be required:

- Documentation of the presence of circulating T1D associated auto-antibodies at diagnosis or at any other time
- History of hospitalization for DKA
- Plasma c-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl)

2.2.2 Advertising

Advertisements may be placed in other health care facilities, college campuses, in local newspapers, and other venues provided the content of these forms of advertising are approved by their clinical center's respective IRB's. Recruitment methods in the form of brochures, flyers, postcards for mailings (letters), or advertising in social media such as Facebook and Twitter will also require IRB approval.

National recruitment strategies, such as the PERL Website, T1D Exchange, GLU, JDRF newsletters, local and national news media are other sources of recruitment strategies which can be utilized to enhance your recruitment efforts.

2.3. Initial Pre-Screening (Identification of Potentially Eligible Subjects):

Patients who are interested in participating will be pre-screened by means of a telephone or in-person interview to determine whether exclusion criteria apply. Patients who respond to advertisements will undergo the same pre-screening interview. Patients who pass this initial pre-screening will be given or mailed an informed consent form and will be invited to come to the clinic for a screening visit (Visit 1)* during which a final eligibility determination will be made. Demographic information, vital signs, anthropometric measurements and laboratory tests will be performed to determine eligibility at this first visit.

***REMOTE SITE VISITS:** If the patient lives far from a study site or satellite, or travel impediments are present, V1 may be conducted remotely. In addition to V1, study visits that may be conducted remotely include V3, V5-10 and V12-15. Visit 2 and all the visits including an iohexol-GFR (iGFR) measurement (i.e. V4, V11, V16 and V17) will always be done "in-person at the Main site or Model 4 satellite.

In the case of a remote visit, study procedures that do not require physical interactions (i.e. demographic information, concomitant medications) will be carried out over the phone or other media, such as Skype (hereby referred to as "Phone Visits"). Blood draws and urine collections scheduled at the time of the Phone visit, will be performed at local facilities close to where the patient lives (hereby referred to as "Remote Biospecimen Collections"). For any given study visit to be conducted remotely, a Phone Visit **and** a Remote Biospecimen Collection will be both required. (Refer to the Protocol 4.1 Location of Study Visits for detailed information).

At the time that **Visit 1** is scheduled, the site should:

- Instruct the patient to bring in the names and dosages of all medications and herbal supplements that they are currently taking.
- If ACR/AER and creatinine measurements are not already available from the clinical site medical records, ask the patient if he/she has had AERs, ACR's and/or serum creatinine levels measured in the last five years by their personal care physician (PCP). If yes, send or hand the patient a "*Release of medical information form*" to obtain a copy of their medical

record. Based on the Urinary Albumin Criteria and the AER/ACR values available during the past 2 years, determine if any urinary albumin measurements are needed to determine eligibility. If additional urinary measurements are needed, send the patient one or two first morning spot urine collection containers along with instructions. Ask the patient to complete the urine collection(s) either the morning of Visit 1 (if only one ACR measurement is needed) or the morning of Visit 1 and the previous morning (if two ACR measurements are needed). The patient needs to bring these samples to Visit 1. Patient Instructions for Spot Urine Collections may be found in the Appendix.

NOTE: If a patient does not have any ACR/AER values reported in the previous two years in the microalbuminuria or moderate macroalbuminuria range, and there is now reason to believe that he/she may now be in that range, the patient may submit **three** urine samples to try to fulfill the two out of three inclusion criteria.

Participants may not meet eligibility criteria based on ACR/AER, but may be eligible because they have evidence of declining kidney function. Evidence of declining kidney function is defined as an eGFR (CKD-EPI) decline $\geq 3\text{ml/min}/1.73\text{m}^2$, as estimated from the slope derived from **all** the available serum creatinine measurements (including the one at screening assessment) from the previous 3 years. If at least 3 serum creatinine measures are not available in the previous 3 years, then the slope can be derived from creatinine values up to the previous 5 years. Slopes should be estimated using the Excel eGFR slope calculator available on the PERL website. The eGFR values to include in the calculation should be selected as follows:

- The most recent value is that at screening (local lab).
 - The oldest value is the value closest to 3 years ago that is GREATER or EQUAL to 3 years ago, but is not older than 5 years ago.
 - All other values between the most recent value and the oldest value must be included.
- **Contraindicated Medications or Herbal Supplements:** If at the time of screening, the participant reports that they are taking a contraindicated medication or herbal supplement that may lower uric acid levels, the participant may be rescreened after having discontinued the medication or supplement with the prescriber's approval for at least 1 month.
 - Send/give the patient the PERL Informed Consent Form (ICF) and explain that he/she will need to read the form prior to their visit and bring it with them for discussion.

NOTE: If the patient is conducting the screening visit remotely, the Informed Consent Form **must** first be reviewed and discussed with the patient, and returned to the study site, **PRIOR** to conducting any study procedures. The remote blood collection kit should be prepared and sent to the patient **ONLY** after the signed ICF is received and all questions answered. Please refer to the Central Laboratory Manual – Chapter 2 on Remote blood/urine collection procedures. These instructions apply to those subjects having a remote collection at their PCP, local lab or hospital. Please note there are specific instructions when blood is collected at a Quest Lab.

At this time the Coordinator should:

- List patient demographic information on the PERL Enrollment Study ID Log.

2.4. PERL Pre-Screening Log

All patients who undergo the pre-screening interview should be recorded on the **Pre-Screening Log**. If they do not consent or are found to be ineligible for the study prior to Visit 1 then the reason for not enrolling should be documented. This information is captured in OpenClinica, in real-time (within 48 hours of screening). If a patient signs the Informed Consent and completes any part of Visit 1 they are considered to be “enrolled” in the study.

2.5. Participant Enrollment

A study ID is **not** assigned at the time of the pre-screening telephone interview and no data is entered into the electronic database (OpenClinica).

Study ID numbers are only assigned to participants who sign the informed consent form and either come in for a screening visit (Visit 1) or go to a remote site for Visit 1. At this point the patient will be given a Study ID number and their information will be recorded on the **Enrollment Study ID Log** and their information entered in OpenClinica.

Chapter 3: Study Visit Details

Figure 1. Schedule of events.

Year	1	1	1	1		1	1	1	1	1	2	2	2	3	3	3	3	3	
Week	-12	-9	-7	-3		0	4	16	32	48	64	80	96	11	128	142	156	164	
VISIT	1	2	3	4	4a*	5	6	7	8	9	10	11	12	13	14	15	16	17	
Type of visit: In-person Visit Required (V); Phone Call (C); Other Visit (In-Person or Remote Visit, O)	O	V	O	V	V	C	O	O	O	O	O	V	O	O	O	O	V	V	
EVENT	Screen	Run-in				Allopurinol or placebo												Wash-out	
						RANDO 100 mg	200-400 mg												
Informed Consent	X	x																	
Demographics	x																		
Initial Medical Hx		x																	
Medical Hx and BP Control Review			X	X	(x)		X	X	X	X	X	X	X	X	X	X	X	x	
Concomitant Meds	x	x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	
Blood Pressure and Measurements	x	x	(x)	x	(x)		(x)	(x)	(x)	(x)	(x)	x	(x)	(x)	(x)	(x)	x	x	
ECG Report		X		x	(x)							x					x		
Physical Exam		x		(x)	(x)			x				x					x		
Skin Assessment				X	(x)	X	X	X	X	X	X	x	X	X	X	X	x	x	
Eligibility	x			X	(x)	x													
Randomization						x													
Family History				X	(x)														
RAS and BP Med Log		x	x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x	
IGFR Procedure				x	(x)							x					x	x	
PERL Study Drug Prescription						X	x	x	x	x	x	x	x	x	x	x			
Study Drug Compliance							X	X	X	X	X	X	X	X	X	X	x		
CENTRAL LAB																			
Serum uric acid, creatinine, cystatin C	x		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x	
24 HR Urine ACR/AER	X		x	x	(x)			x		x		x		x		x	x	x	
HbA1c	x			x	(x)			x	x	x	x	x	x	x	x	x	x	x	
HLA B*58:01				x	(x)														
IGFR				x	(x)							x					x	x	
NIDDK Repository: serum, plasma, urine				x								x					x	x	
LOCAL LAB																			
Pregnancy test serum HCG	x		X	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test urine dipstick		X		x	(x)							X					x	x	
ALT, K, CBC, creatinine	X		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x	
Multistix spot urine testing	x		x	x	(x)		x	x	x	x	x	x	x	x	x	x	x	x	
Protocol Deviation		x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events		x	x	x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	

3.1. Visit Target Dates and Windows

It is critical that all visits are conducted according to the schedule described in Figures 1 and 2. There are three “time frames” within the study: V1-V5, V5-V16, and V16-V17. The first visit in each time frame is considered as the time 0 for computing the target dates of the other visits in that time frame. For instance, the target date for Visit 2 will be exactly 3 weeks from the date of Visit 1. The target date for Visit 6 will be exactly 4 weeks from the date of Visit 5, etc. Each visit can be conducted within a certain time window around the target date (Figure 2). It is extremely important that all procedures of a given visit are done within the corresponding window. If a visit or any part of it occurs outside the window or is missed, this must be reported as a protocol deviation. If the participant does not want to continue, complete the Final Status eCRF #35.

Visits will be more frequent during the Run-In period as participants will be observed for the effect and toleration of ramipril, irbesartan, or an acceptable alternative and closely monitored for the occurrence of adverse events.

There will be a visit within first 30 days after randomization in order to escalate the allopurinol dosage and closely monitor the occurrence of AEs. After that, participants will have a study visit every 12-16 weeks to monitor their UA levels, renal function, occurrence of AEs, and medication compliance and, if necessary, to perform interventions to improve compliance.

As described above, Visit 1 will be considered as Time 0 for scheduling Visits 2-5, Visit 5 will be considered as Time 0 for scheduling Visit 6-16, and Visit 16 as Time 0 for scheduling Visit 17. The study windows that define when study visits may occur are noted in Figure 2 and differ by type of visit. Visits 2, 3, and 6 will be carried out within 6 business days (before or after) from their scheduled dates; visits 11, 16, and 17 within 2 weeks before and 4 weeks after their scheduled dates; visit 4A (if necessary) within 1 week before and 3 weeks after its scheduled date, and all other visits within 2 weeks (before or after) from their schedule dates. The entire study period could be up to 184 weeks if visits are scheduled at maximum windows.

Please note that, even if a subject is not required to be seen in-person at a PERL study site (i.e. a physical interaction is not required – V1, V3, V5-10 and V12-15), all visit procedures are still required and must be carried out over the phone or other media such as Skype if they are not done in person. In this case, blood draws and urine collections scheduled at the time of Phone Visits will be performed at local facilities close to where participants live. For any given study visit to be conducted remotely, a Phone Visit **and** a Remote Biospecimen Collection will be both required.

Figure 2. Study Visit Windows

Visit	# Weeks from Time 0 Visit	Window
Visit 1	0 weeks	NA
Visit 2	3 weeks	± 6 business days
Visit 3	5 weeks	± 6 business days
Visit 4	9 weeks	± 2 weeks
Visit 4a (as needed)	2 weeks from Visit 4	+ 2 weeks
Visit 5	12 weeks + Visit 4a time	± 2 weeks
Visit 5 becomes Time 0 for Visit 6-16		
Visit 6	4 weeks	± 6 business days
Visit 7	16 weeks	± 2 weeks

Visit 8	32 weeks	± 2 weeks
Visit 9	48 weeks	± 2 weeks
Visit 10	64 weeks	± 2 weeks
Visit 11	80 weeks	-2 weeks/+ 4 weeks
Visit 12	96 weeks	± 2 weeks
Visit 13	112 weeks	± 2 weeks
Visit 14	128 weeks	± 2 weeks
Visit 15	142 weeks	± 2 weeks
Visit 16	156 weeks	-2 weeks/+ 4 weeks
Visit 16 becomes Time 0 for Visit 17		
Visit 17	164 weeks	-2 weeks/+ 4 weeks

NOTE: For those patients eligible for skipping V2-V3 (refer to Section 8.3 of the protocol), Visit 4 will be scheduled 3 weeks after V1 with a window of 2 weeks before and 3 weeks after the target date.

3.2. Screening Visit (Run-in Visit 1)

Patients who have a confirmed history of micro-or macroalbuminuria (at least two out of three consecutive urinary AER or ACR in micro-or macroalbuminuria range, will not need to bring a sample of urine to Visit 1. Patients who have incomplete or no previous evidence of micro-or macroalbuminuria or have unknown albuminuria status, will be mailed two or three containers before Visit 1 (depending on the number of desired ACR measurements) along with instructions for collecting two samples of urine from their first morning void and bringing it to the visit to confirm the presence of micro-or macro-albuminuria. The urine samples should be collected the day before and the day of their appointment and kept refrigerated or on ice until they are brought to the clinic (if a third sample is required, this should be collected two days before the day of the appointment). (Refer to Section 4.1.5)

Explain the purpose of the study and review the informed consent document with the patient. If they agree to participate in the study, have him/her sign the informed consent form (ICF). File the original in the participant's research file and give a copy to the participant. At this initial visit study, patients should be encouraged to ask questions and be reassured that they may withdraw from the study at any time. Once the ICF has been signed, the participant can be enrolled into the study database (OpenClinica) and a Study ID will be assigned. Record this information on the Randomization Number Log.

During this visit, participants will undergo the following procedures:

- Obtain written informed consent.
- Collect prior and concomitant medications, and demographic information.
- Review the fetal risks of RAS blockade.
- Counsel female participants on acceptable contraceptive methods.
- Measure weight, BMI, and height.
- Measure vital signs*.
- Perform Urine Multistix.
- Collect samples for clinical laboratory assessment, including a serum pregnancy test

in women of childbearing potential.

- Upon receipt of laboratory measurements, confirm that inclusion/exclusion criteria are met.

***NOTE:** The Screening Visit can be repeated after 4 weeks if the circumstances that led to the exclusion of a participant are deemed to have possibly changed (Please refer to specific circumstances below for guidance on when to rescreen). If a subject is being considered for re-screening, please complete eCRF # 001-RS to indicate the subject will be re-screened. Form 001S should be completed except for the indication of the specific inclusion/exclusion criterion that is being re-evaluated at the re-screen visit; after final eligibility has been determined as a result of the re-screen visit, form 001S can be updated and finalized.

Participants who are interested in continuing the study can be scheduled for Visit 2. When scheduling the visit, participants need to be aware that the appointment is based on meeting all of the criteria completed at Visit 1, and if they do not meet the screening criteria they will be notified prior to the visit.

If the participant is found to be ineligible after Visit 1, and no re-screening is being considered, communicate this to him/her by phone and complete the Eligibility eCRF #001S, Demographics eCRF #002 and the Final Status eCRF # 35. Send a follow up letter thanking them for their willingness to participate. Send a status letter to the PCP if appropriate.

3.2.1. Re-screening:

Re-screening to re-assess the eligibility of potential PERL participants is allowed (see Section 8.2), but the following limits apply to the *number of times* that a subject may be re-screened and the *time frame between assessments* are set, so that the integrity of the clinical trial is not compromised and the statistical power is not unduly affected.

Contraindicated Medications or Herbal Supplements: If at the time of screening, the participant reports that he/she is taking a contraindicated medication or herbal supplement that may lower uric acid levels, the participant may be rescreened after having discontinued the medication or supplement for at least 1 month, with the prescriber's approval.

Uric Acid: If the serum UA criterion is not met at screening (Visit 1), then the subject may be re-screened for this parameter **one** additional time, after at least 4 weeks and no later than 6 months after the first assessment. Per study protocol (Section 8.2), patients on Losartan with uric acid levels between 4.2-4.4 mg/dl at initial screening may, with the agreement of the patient and their PCP, be switched to another angiotensin receptor blocker (ARB) and have their uric acid level re-checked in one month.

eGFR: If the eGFR criterion not met at screening, then **one** additional eGFR measurement may be obtained after at least 4 weeks.

eGFR slope: If the eGFR slope criterion is not met during pre-screening (i.e. EMR values), **one** additional eGFR value for slope calculation may be obtained after waiting at least 6 months.

AER/ACR: If one of the last two AER/ACR's is in the microalbuminuric range at screening, **one** additional AER/ACR may be obtained after at least 4 weeks and no later than 3 months later to determine if the threshold of 2 of 3 sequential abnormal values is met. Complete

retesting of albuminuria status requiring of 2 of 3 sequential abnormal values can be done **once** after waiting at least 6 months.

Blood Pressure: Blood pressure eligibility criteria are assessed at the screening visit (Visit 1) and at the end of the Run-In period (Visit 4). If the BP limits are not met at Visit 1, the patient will be referred to their primary physician for blood pressure management. The participant may then be re-screened **two** additional times at least 4 weeks and no later than 6 months after the Visit 1 assessment. If criteria are not met at Visit 4, then the participant may be re-assessed at Visit 4A, two weeks after the Visit 4 assessment (see Section 8.3).

Safety Tests: If safety parameters (e.g. ALT [SGPT], hemoglobin, platelet count) thresholds are not met at the time of a screening visit, then the participant may be assessed **one** additional time if there is reason to believe that the medical condition (for example, anemia or thrombocytopenia) has resolved or improved, after at least 4 weeks and no later than 6 months after the first assessment. If persistent abnormalities are found, independent expert opinion can be obtained as to the patient's suitability for the trial and, if considered suitable by this expert, their written opinion can be presented to the Exemptions Committee for final decision as to eligibility.

IMPORTANT: If a participant is re-screened for a specific eligibility criterion within 3 months from the initial screening visit, the tests that met the eligibility criteria at the initial screening will be considered to be valid and therefore will not have to be repeated. If a participant is re-screened 3 months or longer after the initial screening visit, the **entire** panel of Visit 1 tests will have to be repeated and eligibility re-evaluated according to all inclusion/exclusion criteria.

NOTE: If the participant is going to be rescreened, the Coordinator should contact the Central Lab, so new labels can be printed for the Rescreen Visit (Visit 1A). The site should notify the Central lab at least one week prior to the rescreen visit, so the new labels can be printed and mailed to the site.

If the participant is found to be ineligible after Visit 1A, communicate this to him/her by phone and complete the Eligibility eCRF #001S and the Final Status eCRF # 35. Send a follow up letter thanking them for their willingness to participate. Send a status letter to the PCP if appropriate.

3.3. Run-In Visit 2

Starting at Visit 2, eligible subjects who agree to participate in the study will enter the Run-in period of 9 weeks. (See note at the end of this section for exceptions to this duration). During this visit, subjects will undergo the following procedures:

- Obtain written informed consent to enter run-in period (if the consent at V1 was only for screening).
- Collect medical history, especially **any** possibility of pregnancy.
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Collect information on concomitant medications.
- Review the fetal risks of RAS blockade.

- Measure height, weight, and BMI.
- Record BP and pulse following the study specific BP procedure (Refer to MOO Chapter 4.3).
- Complete Physical Exam.
- Perform ECG.
- Perform urine Multistix and urine pregnancy test.
- Blood Pressure Management:

RAS antagonist treatment will be standardized, and BP, if elevated (>140/90 mmHg), normalized. Letters will be written to the participant's physician(s) informing them about the study, and notifying them of the study's protocol RAS Blocker requirements and blood pressure goals. The letter will propose active participation of the patient's physician(s) in blood pressure management with the availability of advice from the PERL site physicians and, if needed the PERL Drug Monitoring Committee for out of range blood pressure values during the course of the study. The Run-In period will start at Visit 2.

 - If the participant is already on a RAS Blocker, the dose will be increased, if necessary, to make it at least equivalent to Ramipril 10mg (if on ACE inhibitor [ACEi]) or Irbesartan 300 mg (if on an angiotensin receptor blocker [ARB]), if acceptable to the patient's primary physician, if tolerated, and if not contraindicated.
 - Participants who are not taking a RAS Blocker and do not have contraindications to this therapy will be prescribed and instructed to start taking 10mg of Ramipril daily or 300 mg of Irbesartan daily (if Ramipril is contraindicated or has side effects) or another ACE inhibitor or ARB at equivalent doses if there are impediments to the use of Ramipril or Irbesartan.
 - Participants who are placed for the first time on RAS Blockers as part of this study will start with half a dose; if there are no side effects, this will be increased to a full dose at Visit 3, and their serum K⁺ and creatinine measured at a local laboratory after 2 weeks. This will be paid for by the PERL study.
 - Participants who have contraindications to RAS Blockers (e.g. SPB <100 mmHg, K⁺ 5.5mEq) will not be treated with these drugs, as this represents the standard of care.
 - Please Refer to MOO Chapter 4.6 for further details about Blood Pressure Management and RASB therapy.
- If the participant is willing to proceed, schedule Run-In Visit 3.
- Give participant Overnight Urine Collection Instructions (Refer to Patient Instructions for Timed Urine Collection in Appendix) and urine jug (include hat for females if needed) for AER for Visit 3.
- Provide participant with BP monitor and instructions for use (if they do not already have access to one). (Refer to Patient Instructions in Appendix)
- Provide PERL study information (if not given at Visit 1) including a visit schedule calendar, BP logs, staff phone numbers, site map and parking instructions, business card and other pertinent study information.

NOTE: The participant will decide whether or not the clinical information gained at study visits is to be shared with their personal care physician (PCP). If they agree to have this information shared, make sure they have checked the appropriate box and signed the appropriate line in the "*Confidentiality Section*" of the ICF. If the participant has agreed, notify the PCP that their patient has agreed to participate in the study and has entered screening. PCP's are asked to avoid prescribing drugs that would interact with ramipril or

other ACEIs or ARBs, depending on the RASB they are on, and/or allopurinol. Ask that they also notify the study personnel if they feel that treatment with such drugs is necessary. (Refer to Letter Templates in the Appendix).

IMPORTANT: Visit 2 and Visit 3 can be skipped (i.e., a participant can move directly from Visit 1 to Visit 4) if the following criteria are met at Visit 1:

- The participant is eligible based on the results of Visit 1 assessments, including laboratory values:
- Blood pressure is < 140/90 mmHg: AND
- The participant meets **one** of the following criteria:
 - Has been treated with a RASB for at least two months at a dose at least equivalent to Ramipril 10mg or Irbesartan 300mg
 - Has contraindications to RASB
 - Does not have evidence or history of micro or macroalbuminuria (as defined in Section 5.1.4) and is not being treated with RASB or other antihypertensive agents.

If the above criteria are met and Visit 2 and Visit 3 are skipped, Visit 4 will be scheduled 3 weeks after Visit 1, with a window of 2 weeks before and 3 weeks after the target date. Skipped V2 and V3 is captured in OpenClinica on eCRF # 001S under eligibility. Documentation of the reason why the participant is eligible to skip V2/V3 should also be noted in the patient's binder, or using the optional Worksheet #001Sk. The signature of the physician is required on this form to verify that the patient is in fact eligible to skip these two visits.

If Visit 2 and Visit 3 are skipped, the collection of Medical History and Physical Exam scheduled at Visit 2 will be conducted at Visit 4. The urine collection that was scheduled at V3 will take place at V4 (this means that the participant will do two urine collections for V4, one on the day before V4, and the other will be one or two days before that).

NOTE: If the site chooses to bring the patient in for V2, then a V3 must also take place, otherwise it should be recorded as a protocol deviation, and the site should complete Worksheet #40 and eCRF #40. The site also has the option to file for an *Exemption Request* in this instance. An example of this may occur if, for example, the patient was seen remotely for V1, and the Site physician would like to verify eligibility at V2 before skipping V3.

3.4 Run-In Visit 3

- Review interval medical history (with special emphasis on CVD events and any possibility of pregnancy).
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Review RASB and BP therapy.
- Review any change in concomitant medications
- Measure weight and BMI. (optional if a remote visit).
- Record BP and pulse following the study specific BP procedure (optional if a remote visit)
- Collect blood and urine samples for local and central laboratory assessments, and urine Multistix testing as outlined in Figure 1.

- Provide a container and instructions for an overnight urine collection to be made immediately before Visit 4 (Refer to Patient Instructions in the Appendix).
- Schedule Visit 4. If possible, schedule the iGFR appointment early in the morning and ask the patient if they are able to fast for 8 hours. NOTE: Fasting is not required, however, is recommended. Participants should be advised to avoid use of NSAIDs (Advil, Motrin, Aleve, Ibuprofen) for 3 days prior to iGFR (Tylenol and Aspirin are OK), and to avoid strenuous exercise and large protein meals 24 hours prior to Visit 4. Provide participant instructions for iGFR procedure (Refer to Patient Instructions in the Appendix).
- If participant was started on a RASB at Visit 2, and if there were no side effects, the dose should be increased to full dose. Serum K+ and Creatinine need to be tested in local lab after two weeks on full dose.

Iohexol is an iodine-based solution so it is imperative that the patient not have an allergy to iodine-based contrast media as iohexol is such a product and will be administered during the iGFR testing. NOTE: A seafood allergy is NOT exclusionary.

3.5 Run-In Visit 4 (or 4a)*

- Review interval medical history (with special emphasis on CVD events and any possibility of pregnancy).
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Review RASB and BP therapy.
- Review any change in concomitant medications
- Measure height, weight, and BMI.
- Record BP and pulse following the study specific BP procedure**
- Conduct a physical exam (if deemed to be required by the study physician)*.
- Conduct baseline skin assessment. Instruct participant on how to perform self-skin assessment and provide instructions for interim study visits. (Refer to Patient Instructions in the Appendix).
- Perform ECG.
- Collect blood and urine samples for local and central laboratory assessments (including HLAB*58:01), urine Multistix testing and biomarker research blood samples, as outlined in Figure 1. If the patient has arrived fasting, baseline blood samples should be drawn in the fasting state.
- Perform urine pregnancy test in women of childbearing potential **prior to** iGFR test.
- Perform iohexol GFR testing. Refer to PERL MOO Chapter 4, as well as Nursing Iohexol Worksheet #18 and iGFR Physician Orders. Record any Adverse Events during the procedure. Instruct participant to increase fluids for the remainder of the day to flush out the iohexol.
- Following the iGFR, instruct the participant to drink plenty of fluids for remainder of day to flush out Iohexol.

*For subjects that were deemed eligible to skip the Run-In period (Visits 2 and 3), please also complete the Medical History (CRF #003) and physical exam (CRF #007) at this visit, as these would have otherwise been completed at Visit 2.

****If normal blood pressure control is not achieved at Visit 4, the run-in period may be extended for two more weeks after which participants will be examined as in Visit 4 (Visit 4A). (Visit 4a is reserved ONLY for this purpose). In this event, the**

iGFR measurement scheduled for Visit 4 will be conducted at Visit 4A. Participants whose SBP is >150 or whose DBP is >95 mmHg at the end of the run-in period will be discontinued from the study (prior to randomization).

In the event of an invalid iGFR (which results in an r^2 value of ≤ 0.9), source documents related to the test in question will be reviewed to verify whether there was a protocol deviation or technical error in the iGFR procedure (i.e. presence of contraindications to iGFR, swapping of tubes, wrong collection times, typos, ect...) In the case of an $r^2 \leq 0.90$, the iohexol measurements will be repeated by the Central Lab. (Refer to Section 7.1.3 of the Protocol)

If an error is confirmed, and cannot be fixed, or no error can be found, the iGFR will be dropped and the participant should be brought back in for a repeat iGFR within 4 weeks from when the iGFR results became available.

This repeat iGFR visit will be completed as an *unscheduled visit*. If the participant is brought back within 3 months of Visit 4 (or V4a), then *only* the iGFR procedure needs to be repeated.

3.6. Randomization Visit 5 (Phone Visit)

At the end of the run-in period, eligibility will be re-assessed based on the BP measurements obtained at Visits 4 or 4A (if applicable), HLA-based genetic susceptibility to allopurinol skin reactions (tested at Visit 4), and a valid baseline iGFR measurement. Participants who are eligible for randomization based on those measures (SBP ≤ 150 and DBP ≤ 95 mmHg) and a negative HLA B*58:01 test will be telephoned by the study coordinator to discuss how the study medication should be taken and its potential side effects. Review history for any possibility of pregnancy, and do not randomize if pregnancy is suspected until a negative pregnancy test has been obtained. No in-person contact is required for this visit.

Before the call

- Confirm Inclusion/Exclusion criteria. If the participant is positive for HLA-based genetic susceptibility to allopurinol skin reactions, or unacceptable BP measurements or a valid iGFR measurement cannot be obtained, he/she will not be randomized into the study.
- eCRF #001R form must be entered into OpenClinica at least 24 hours in advance of randomization.

During the call

- Verify participant agrees with conditions in ICF and is willing to proceed with randomization.
- Instruct participant that study medication will arrive in the mail, and that they should notify the Study Coordinator when the medication is received, and begin taking it as soon as it is received.
- Discuss pill taking instructions and side effects (Refer to Patient Instructions in the Appendix).
- Instruct participant to write start and end date of the pill bottles on the label
- Remind the participant of the importance of performing self-skin examination and to notify the study staff immediately of rash.
- Instruct patients to discontinue study medication and RASB and notify the study staff immediately if there is a possibility of pregnancy.
- Schedule Visit 6.

After the call

- Immediately after the phone call, participants will be randomized in OpenClinica (refer to MOO Chapter 9) for the Randomization Procedure).
- Complete the PERL Study Drug Prescription and have it signed by the Study Physician, as well as complete the PERL Study Drug Shipping Notification Form. Both forms should be faxed to the Pharmacy. Once received, the first batch of study medication will be shipped to the participant by the research pharmacy along with written instructions on how to take it (refer to MOO Chapter 7 regarding Study Drug Process and Information).
 - Instruct the participant to notify the Study Coordinator when the medication is received and to begin taking it as soon as it is received.
 - Provide written pill taking instructions and side effects (Refer to Patient Instructions in the Appendix).
 - Instruct participant to write start and end date on the pill bottles on the label.
 - Instruct participant not to discard ANY pill bottles. Inform the participant that at their next scheduled visit, they will be provided with a stamped self-addressed envelope to return the current pill bottles when the new batch of study medication has been shipped to them.
 - Remind the participant of the importance of performing self-skin examination and to notify the study staff immediately of rash
 - Send PCP a letter notifying them that the participant has been randomized.
 - Schedule Visit 6
 - The participant should be called within a week of randomization to verify that they have received their study pills from the pharmacy. Review pill taking instructions to be sure they understand how to take them correctly.
 - Instruct patients to discontinue study medication and notify the study staff immediately if there is a possibility of pregnancy

3.7. Treatment Period –Visits 6-15

During the treatment period, the following procedures will be completed at each visit for each participant:

- Review interval medical history (with special emphasis on CVD events and any possibility of pregnancy).
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Review RASB and BP therapy.
- Review any change in concomitant medications
- Measure height, weight, BMI, and vital signs according to the schedule outlined in Figure 1 (optional at V6-10 and 12-15 if conducted remotely).
- Conduct a physical exam (Visit 11).
- Inspect for skin rash. In the case of visits done remotely, participants are to perform self-skin assessment for each scheduled study visit, and return the completed worksheet to the Study Coordinator for documentation. *Suspicion of drug allergy or Stevens - Johnson syndrome (SJS) would require **immediate** discontinuation of study medication and dermatologic consultation.* Any such case should be submitted to the PERL Drug Monitoring Committee for review.
- Perform ECG (Visit 11).
- Perform urine Multistix (V6-15)

- Collect samples for clinical laboratory assessments and for storage of serum, plasma and urine for later biomarker research according to the schedule outlined in Figure 1.
- Perform urine pregnancy test in women of childbearing potential **prior to** iGFR test (Visit 11), and serum pregnancy test at all visits (according to the schedule outlined in Figure 1)
- Perform iohexol iGFR testing at visit 11. Refer to PERL MOO Chapter 4, as well as Nursing Iohexol Worksheet #18 and iGFR Physician Orders. Record any Adverse Events during the procedure.
- Provide a container and instructions for an overnight urine collection whenever an AER measurement is scheduled at the following visit. (AER at Visits 7, 9, 11, 13, 15, and 16).
- Obtain results of local serum Creatinine and fax PERL Study Drug Prescription and Shipping Notification Form to Central Pharmacy.
- Provide participant with a self-addressed stamped envelope to return their left over pills.
- Once any unused study medication is received from the subject, document compliance on Worksheet #22 and eCRF #22.

3.7.1 Study Medication Resupply

In the days immediately after each visit, upon completion of **local** serum creatinine measurements, participants will receive a new batch of study medication by mail from the research pharmacy. Upon receipt of the new tablets, participants will be instructed to write the START date on the new bottle, and indicate the END date on the current bottle, and immediately mail the pill bottles with the tablets remaining from the previous prescription to the coordinator for drug accountability and compliance assessment. The coordinator will provide a pre-stamped and addressed envelope to participants for this purpose. Document study drug compliance on Worksheet #22 and eCRF #22 (See 7.4 and 7.5 for detailed instructions on returning these meds to the Central Pharmacy.

3.8. End of Intervention (Visit 16)

At the end of the treatment period (Visit 16), the following procedures will be completed for each participant:

- Review interval medical history (with special emphasis on CVD events and any possibility of pregnancy).
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Review RASB and BP therapy.
- Review any change in concomitant medications.
- Collect unused study medication and document compliance on Worksheet #22 and eCRF #22.
- Measure height, weight, BMI, and vital signs.
- Conduct a physical exam.
- Inspect for skin rash.
- Perform ECG.
- Collect samples for clinical laboratory assessments and for storage of serum, plasma and urine for later biomarker research according to the schedule outlined in Figure 1.
- Perform urine Multistix.
- Perform urine pregnancy test in women of childbearing potential **prior to** the iGFR test.
- Perform iohexol GFR testing. Refer to PERL MOO Chapter 4, as well as Nursing Iohexol Worksheet #18 and iGFR Physician Orders. Record any Adverse Events during the procedure. Instruct participant to increase fluids for the remainder of the day to flush

out the iohexol.

- Provide containers and instructions for **2 overnight urine collections** to be made immediately before Visit 17. (Refer to Patient Instructions for 24-hour Urine Collection)

Participants will be instructed to **stop taking the study medication** and to mail the pill bottles with the tablets remaining from the last prescription to the study center if they did not already bring the unused study medication to the visit. In this case, provide the participant with a self-addressed, stamped envelope. **The RAS and BP therapy will be continued as before until the closing visit (Visit 17).** The importance of coming back in 8 weeks for the closing visit (Visit 17) should be emphasized.

3.9. End of Wash-out Period (Visit 17)

After the end of the treatment period, participants will enter an 8-week wash-out period at the end of which the following procedures will be completed:

- Review interval medical history (with special emphasis on CVD events and any possibility of pregnancy).
- Document any adverse events (Complete eCRF #20 and/or 45) or protocol deviations (Complete eCRF #40).
- Review RASB and BP therapy.
- Review any change in concomitant medications.
- Measure height and weight, BMI, and vital signs.
- Inspect for skin rash.
- Collect samples for clinical laboratory assessments and for storage of serum, plasma and urine for later biomarker research according to the schedule outlined in Figure 1.
- Perform Urine Multistix
- Perform urine pregnancy test in women of childbearing potential **prior** to iGFR.
- Perform iohexol GFR testing. Refer to PERL MOO Chapter 4, as well as Nursing Iohexol Worksheet #18 and iGFR Physician Orders. Record any Adverse Events during the procedure. Instruct participant to increase fluids for the remainder of the day to flush out iohexol.

3.10. Unscheduled Visits

An Unscheduled visit may be required at any time during the study for possible lab re-draws or other necessary safety procedures. Any of the follow procedures may be required during an unscheduled visit:

- Change in medical history
- Evaluation of Adverse Event or Severe Adverse Event.
- BP measurements or change in BP medications
- Physical Exam
- Skin Assessment
- ECG
- Lab (local and/or central)
- Pregnancy testing
- Complete iGFR procedure

3.11. Lost to Follow-Up/Inactive

A subject is designated as “**currently inactive**” if the site is not able to establish contact with the subject for >8 months despite the following steps documented in the subject’s binder:

- 3 or more failed attempts to contact the subject and/or their designated contact by telephone
AND
- 3 or more unreturned e-mails to the subject at their provided e-mail address (if applicable),
AND
- No response to a letter sent via certified mail, which should be sent 2 weeks after the third unreturned e-mail (or phone call if no e-mail address provided).

3.11.1. Currently Inactive Subject Reporting Guidelines:

When a site has determined that a subject is currently inactive by the above criteria, this should be indicated on the Final Status Form (Form 035) as follows:

- In Section A2, select the "other" option
- In the "Other, Specify" text box, type the words "currently inactive"
- Save the form

NOTE: If the site is certain that a subject will not return to the study, "Lost to Follow-up" can be selected in Section A2 instead of "Other". Note that at some sites the IRB rules dictate that such a designation mandates that the sites make no further efforts to contact the patient. Please check your IRB's policy in this regard.

NOTE: If the subject is deemed "currently inactive" and later returns to the study, the site should contact the DCC in writing and the DCC will modify the Final Status Form accordingly.

Chapter 4

Study Procedures

4.1. Urine Albumin and eGFR Criteria and Procedures

4.1.1. Determination of eligibility based on AER/ACR values and eGFR slope.

Participants can qualify for the study because they have a **history or presence of microalbuminuria or moderate macroalbuminuria** *OR* because they show evidence of **declining kidney function** *without* a history or presence of albuminuria and/or therapy with RAS Blockade (RASB) agents.

Micro- or moderate macroalbuminuria is defined as at least two out of three **consecutive** urinary albumin excretion rates [AERs] or albumin creatinine ratios [ACRs] taken during the two years **before screening or at screening**, that meet the following criteria:

1. AER's in the 30-5000 mg/24 hr or ACR's in the 30-5000 mg/g range if **not on RASB agents**.
2. AER's in the 18-5000 mg/24 hr or ACR's in the 18-5000 mg/g range if **on RASB agents**.

Declining kidney function is defined as an eGFR (CKD-EPI) decline ≥ 3.0 ml/min/1.73 m²/year estimated from **all** the available creatinine measurements (**including the one at screening assessment**) from the previous 3 years. If at least 3 serum creatinine measures are not available in the previous 3 years, then the slope can be derived from creatinine values from up to the previous 5 years. An EXCEL-based slope calculator is available on the PERL website. The eGFR values should be used to calculate the slope according to the following criteria:

- Most recent value is from screening (**local lab value**)
- The oldest value is the value that is closest to 3 years that is GREATER or EQUAL to 3 years ago, but no more than 5 years ago
- All other values between the most recent value and the oldest value should be used

4.1.2. Fulfilling the AER/ACR criteria for eligibility

For eligibility purposes, a subject may fulfill the criteria in the following ways:

1. Subject had two out of three consecutive AER/ACR's done during the past two years (i.e., before the study) at the Clinical Site or by other health care providers in the target micro-/macroalbuminuria range.
2. Subject had the second to last AER/ACR done in the past two years (i.e., before the study) at the Clinical Site or by other health care providers in the target micro-/macroalbuminuria range and has an ACR performed at Visit 1 that is also in the target micro-/macroalbuminuria range. (Note that if there are only two values in the last two years and both meet eligibility criteria, a third value at Visit 1 is not needed for eligibility). If only one was done in the past two years and was in the microalbuminuria range and the first one by the PERL study is in the normoalbuminuric range, a third sample will be needed to determine eligibility (see below).
3. Subjects had the last or the only AER/ACR done in the past two years (i.e., before the study) at the Clinical Site or by other health care providers in the target micro-

/macroalbuminuria range, and has one out of two ACR's performed at Visit 1 also in the target micro-/macroalbuminuria range. (Note that if the previous values were close to the microalbuminuria range and the eGFR criterion is met, the site may choose to test whether two of three current AER/ACRs meet the entry criteria).

4. Subject has *not* undergone any AER/ACR measurements during the past two years (i.e., before the study) at the Clinical Site or by other health care providers in the target micro-/macroalbuminuria range, and have two out of three ACR's performed at Visit 1 also in the target micro-/macroalbuminuria range.

4.1.2.1. Determining Eligibility according to criteria No. 1:

If the AER/ACR eligibility criteria are met according to No. 1 above, the subject qualifies for screening purposes and will **not need to do another urine collection until Visit 3**, at which time they will bring in an overnight timed urine collection for one of the baseline AER's.

4.1.2.2. Determining Eligibility according to criteria No. 2:

If the eligibility criteria are *not* met according to No. 1 above, the subject can have **the second to last AER/ACR done during the past two years** (before the study) at the Clinical Site or by other health care providers in the target micro-/macroalbuminuria range, and one first-morning void spot urine collection in the target micro-/macroalbuminuria range **at the Screening Visit (Visit 1)**. To qualify in this manner, the subject should be asked to do a first-morning void, clean catch, midstream urine sample collection for an ACR the morning of **Visit 1**.

4.1.2.3. Determining Eligibility according to criteria No. 3:

If the eligibility criteria are *not* met according to No. 1 or 2 above, the subject can have **the last or the only AER/ACR done during the past two years** (before the study) at the Clinical Site or by other health care providers in the target micro-/macroalbuminuria range, and one out of two first-morning void spot urine collections in the target micro-/macroalbuminuria range **at the Screening Visit (Visit 1)**. To qualify in this manner, the subject should be asked to do **two** first-morning void, clean catch, midstream urine sample collections for ACR, **one on the morning of Visit 1 and one on the morning before the appointment** and bring them to Visit 1.

4.1.2.4. Determining Eligibility according to criteria No. 4:

If the eligibility criteria are *not* met according to No. 1, 2, or 3 above, the subject can have **two out of three AER/ACR done at the Screening Visit (Visit 1)** that are in the target micro-/macroalbuminuria range. To qualify in this manner, the subject should be asked to do **three** first-morning void, clean catch, midstream urine sample collections for ACR, **one on the morning of Visit 1 and the other two on the preceding 2 mornings before the appointment**.

If none of these four approaches lead to fulfillment of the ACR/AER criteria, the patient is ineligible based on ACR/AER, and you should determine if the patient is eligible based on eGFR slope. (See 4.1.3. below).

Figure 1. Examples of eligible subjects (ACR/AER in the target range are indicated in red).

- If **two out of three consecutive** ACR/AER measurements are in the target range, the subject is eligible.
- If **one out of two** consecutive ACR/AER measurements is in the target range, a 3rd urine meeting the criteria is required.

Figure 1

NOT on RASB Agent		ACR from medical records in the preceding 2 yrs (mg/g)					ACR at screening (mg/g)	
		9/2011	9/2011	11/2011	12/2011	1/2012	4/2013	9/2013
1	OK	10	12	40	35	15	24	28
2	OK	10	12	12	35	13	40	25
3	OK	10	-	-	-	35	12	35
4	OK	10	12	12	13	40	15	35
5	NO	10	12	40	13	15	24	26
6	NO	10	12	12	13	15	40	25
7	OK	500	750	600	1000	1500	750	900
8	OK	500	750	600	1000	1200	2300	2500

ON RASB Agent		ACR from medical records in the preceding 2 yrs (mg/g)					ACR at screening (mg/g)	
		9/2011	9/2011	11/2011	12/2011	1/2012	4/2013	9/2013
1	OK	10	12	19	35	15	24	28
2	OK	10	12	12	35	13	40	25
3	OK	10	-	-	-	35	12	35
4	OK	10	12	12	13	40	15	35
5	NO	10	12	40	13	15	24	26
6	NO	10	12	12	13	15	40	25
7	OK	500	750	600	1000	1500	750	900
8	OK	500	750	600	1000	1200	2300	2500

4.1.3. Determining eligibility based on slope:

Subjects may also qualify for the study because they show evidence of declining kidney function based on eGFR slope, regardless of the presence of microalbuminuria or moderate macroalbuminuria.

Evidence of declining kidney function is defined as an eGFR (CKD-EPI) decline of ≥ 3.0 ml/min/1.73m² year, estimated from the slope derived from *all* the available serum creatinine measurements (*including the one at screening assessment*) from the previous 3 years. If at least 3 serum creatinine measures are not available in the previous 3 years, then the slope can be derived from creatinine values from those done in the the previous 5 years.

To determine eligibility based on eGFR slope:

1. Gather ALL serum creatinine values, including the one at the screening visit (**local lab**), from the previous 3 years. If at least 3 are not available, then the slope can be determined from creatinine values up to 5 years. A copy of the Creatinine source documentation must be maintained in the participant's binder.
2. Determine eGFR values, using the CKD-EPI Creatinine Calculator. This calculator is located in the National Kidney Foundation website at:

http://www.kidney.org/professionals/KDOQI/gfr_calculator

The link is also provided on the PERL Website and in the Coordinator DropBox.

To determine the eGFR slope, you will need the following information in determining eGFR:

- **Creatinine value and date**
- **Age**
- **Race**
- **Gender**

Choose CKD_EPI Creatinine equation. The value measurement will be in ml/min/1.73m².

3. Open the appropriate eGFR Slope Calculator (Excel file) located in the Coordinator DropBox and follow the instructions. (see below) The calculator will automatically calculate the slope and indicate if the participant is eligible or not.
4. Document the eGFR slope value on **eCRF #16 ACR/AER**.
5. Print out the calculations, and place a copy in the participant's chart. Upload the calculations to OpenClinica.

PERL Study									
Calculation of the eGFR slope for inclusion, if evidence of micro-/macroalbuminuria is old and the patient is currently normoalbuminuric									
Version 7.0									
The specific inclusion criterion from the protocol (Version 7.0) is:									
History or presence of microalbuminuria or moderate macroalbuminuria, or evidence of declining kidney function regardless of history or presence of albuminuria and/or RAS Blockade. Micro- or moderate macroalbuminuria will be defined as at least two out of three consecutive urinary albumin excretion rates [AERs] or albumin creatinine ratios [ACRs] taken during the two years before screening or at screening in the 30-5000 mg/24 hr or 30-5000mg/g range, respectively, if not on RASB agents, or in the 18-5000 mg/24 hr or 18-5000 mg/g range, respectively, if on RASB. Evidence of declining kidney function will be defined as an eGFR (CKD-EPI) decline $\geq 3\text{ml}/\text{min}/1.73\text{m}^2$, estimated from all the available creatine measurements (including the one at screening assessment) from the previous 3 years. If at least 3 serum creatinine measures are not available in the previous 3 years, then the slope can be derived from creatinine values from the previous 5 years.									
The eGFR values that should be used are:									
* most recent value is from screening.									
* the oldest value is the value that is closest to 3 years that is GREATER or EQUAL to 3 years ago, but no more than 5 years ago.									
* all other values between the most recent value and the oldest value should be used.									
INSTRUCTIONS:									
1. Enter Subject ID									
2. Enter the date of each eGFR measurement (using format mm/dd/yyyy).									
3. Enter eGFR values (using CKD-EPI formulas).									
4. The slope will be calculated for you. If it is $\leq -3\text{ ml}/\text{min}/1.73\text{ m}^2$, then the patient is eligible. If the slope is $> -3\text{ ml}/\text{min}/1.73\text{ m}^2$, then the patient is ineligible.									
5. Print out the calculations and place a copy in the participant's binder. Please Upload the calculations to OpenClinica.									
PERL Subject ID: <input type="text"/>									
Enter the following information									
Observation (*need at least 3 values, and oldest value must be at least 3 y and no more than 5 y ago)	<input type="text"/>				<input type="text"/>		Eligible or not		
	DATE of eGFR (mm/dd/yyyy)	eGFR (ml/min/1.73m ²)			slope				
1 - PERL screening									
2									
3*									
4									
5									
6									
7									
8									
9									
10									

4.1.4. Modalities for spot urine collection for ACR measurements at Visit 1.

The subject should be provided with detailed instructions, towelettes for cleaning the genitals, and a sterile urine cup for the collection. The cup containing the specimen should be kept tightly closed and refrigerated, or on ice, until it is handed over at the clinic.

1. The Subjects should be asymptomatic for febrile intercurrent illnesses, urinary tract infection, menstruation, and hematuria.
2. The Subjects should avoid the use of nonsteroidal anti-inflammatory medications (Advil, Aleve, Motrin, etc.) for at least 48 hours prior to the urine collection.

3. The Subjects should avoid strenuous exercise for at least 24 hours prior to the spot urine collection.

At the clinic a Multistix should be done on the specimen and the result recorded. (See Section 4.2 for Instructions).

The site should store an aliquot of the urine until the Creatinine excretion rate is known. If the result is $< 0.4\text{mg/kg(bw)}/\text{hr}$, the collection should be repeated and the overnight urine sample discarded. The urine creatinine result should be recorded on AER/ACR (eCRF #16).

4.1.5. AER Urine Sample Overnight (timed) Collection for measurements of AER as a Secondary Outcome (for *Enrolled Participants*)

1. Subjects should be asymptomatic for febrile intercurrent illnesses, urinary tract infection, menstruation, and hematuria.
2. Subjects should avoid the use of nonsteroidal anti-inflammatory medications (Advil, Aleve, Motrin, etc.) for at least 48 hours prior to the urine collection. Aspirin or Tylenol are OK.
3. Subjects should avoid strenuous exercise for at least 24 hours prior to the urine collection.
4. Subjects will be asked to follow the Instructions for Overnight Urine Collection.
5. The collections must be a ***minimum of 4 hours*** in duration and the subject should record the exact start time and end time for the collection (see Figure 2 below for minute decimals), and have a ***volume of > 150 ml*** (see Parameters for Urine Specimens below).
6. The start date (time when participant empties the bladder and discard urine), end date (last time participants empties the bladder and collect urine), volume (ml) and totals hours of collection should be recorded on the Central Lab Shipping/Mailing List.
7. Collection should be done the night before the appointment. If that is not possible (work schedule, menses, etc., the collection may be done **NO MORE THAN TWO WEEKS** prior to the appointment and must be kept refrigerated until it is brought to the clinic.
8. Specimens should be refrigerated or on ice during the collection and until specimen is delivered to the clinical center. Specimens can be at refrigeration temperatures for a maximum of two weeks.
9. Prior to randomization, subjects will be provided with instructions and a urine jug (including a hat for females, if needed) at Visits 2 and 3 for Visit 3 and Visit 4 to determine their AER baseline values before randomization **NOTE:** Patients eligible to skip V2 and V3 must bring two overnight urine collections to Visit 4. These can be consecutive nights or 2-3 nights apart with samples refrigerated until brought to the V4 appointment.
10. Once subjects are randomized they will be provided with instructions and a urine jug (including a hat for females, if needed) at Visits 6, 8, 10, 12, 14, 15, 16 for Visits 7, 9, 11, 13, 15, 16 and 17 to determine their AER values.

4.1.6. Parameters for urine specimens:

4.1.6.1. Overnight Collections:

The center should store an aliquot of the urine until the Creatinine excretion rate is known. If the result is $< 0.4\text{mg/kg (bw)}/\text{hr}$, the collection should be repeated and the overnight urine sample discarded. The urine creatinine result should be recorded on AER/ACR (Worksheet #16 and eCRF #16).

4.1.6.2. Duration:

Duration of 4 hours minimum is required – ***if collection time is <4 hours***, the collection must be repeated (see Figure 2 below for recording minutes in decimals).

4.1.6.3. Processing and Shipping Instructions for AER/ACR Urine Specimens

1. Prompt processing and preservation of specimens under ideal conditions with secure delivery to the CBL is important in order to maintain the quality of the assays.
2. At the clinic a Multistix (see Section 4.2) should be done on the specimen and the result recorded ***before the participant leaves the clinic***.
3. Assume that all biological specimens may be infectious and, therefore, require protective measures to prevent leakage during shipping. Use the 2.0 ml micro centrifuge tube with yellow cap. Do not fill the tubes with more than 1.75 ml of urine because of expansion when freezing. Ensure that the caps are screwed onto the tubes properly. Secure Zip-Lock bags over the storage boxes to protect against leakage.
4. Do not ship specimens without accompanying PERL Central Lab (CBL) Shipping/Mailing List (Form #37).
5. Ship the frozen **screening** specimens every **Monday or Wednesday** (Tuesday if Monday is a Holiday).
6. Ship **enrolled** study specimens, **frozen**, on dry ice, **every month**. **NOTE:** Ship the available frozen iGFR specimens in the same box with the urine specimens designated for AER. Be sure to use an adequate amount of dry ice. The amount of dry ice in the shipping box should total at least 5 pounds (10 pounds for international shipments). Please refer to Section 5 (Packaging and Shipping) in the *Central Laboratory Biospecimen Collection and Processing Manual* for detailed information.
7. **Use Fed Ex Overnight to ship.**
8. **Shipping address:**

**Naomi Thompson/ PERL Central Biochemistry Laboratory
University of Minnesota
Advanced Research and Diagnostic Lab (ADRL)
1200 Washington Ave, South, Suite 175
Minneapolis, MN 55415
Telephone: (612) 625-5040
Fax: (612) 273-3489**

NOTE: Send an email to notify Anna Lukkari: lukka019@umn.edu; Van Le: lex557@umn.edu and Naomi Thompson: thom4228@umn.edu that a shipment was sent.

Figure 2

Minutes vs Decimals
Use for CBL Shipping/Mailing Form 37

Minutes	Decimal
0-3	.00
4-9	.10
10-15	.20
16-21	.30
22-27	.40
28-33	.50
34-39	.60
40-45	.70
46-51	.80
52-57	.90
58-60	1.00

4.2. Multistix Testing

Multistix are intended for use in aiding in testing for kidney function, urinary tract infections, carbohydrate metabolism, and liver function. The Multitix 10 SG tests for leukocytes, nitrates, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

Multistix testing is performed at **all** PERL study visits, and should be performed at the beginning of the visit. This will insure that appropriate action is taken in the event of a positive result (see section 4.2.3 below for guidance).

The testing strips are ready to use upon removal from the bottle. The strips are read visually.

4.2.1. Specimen Collection and Preparation:

1. Collect freshly-voided urine in a clean container and test it as soon as possible.
2. The container should allow for complete dipping of all reagent strip agents.
3. The **first morning void** specimen is preferred, but random collections are acceptable.
4. Test the urine *within two hours* after voiding, *or sooner if the strip tests for bilirubin or urobilinogen*. If unable to test within the recommended time, refrigerate the specimen immediately, and let it return to room temperature before testing.
5. Work area and specimen containers should always be free of detergents and other contaminating substances.

4.2.2. Procedure:

1. **Collect** a fresh urine specimen in a clean, dry container. **Mix** well just before testing. **Remove** one strip from the bottle. **Replace** the cap.
2. **Dip** all the test pads of the strip into the urine. **Immediately** remove the strip. If reading the strip visually, **start timing**.
3. **Drag** the edge of the strip against the container rim to remove excess urine.
4. **If reading visually:**
 - **Compare** each test pad to the corresponding row of color blocks on the bottle label.
 - **Read** each pad at the time shown on the label, starting with the shortest time. (i.e.) 30, 40, 45, or 60 seconds, or 2 minutes.
 - **Hold** the strip close to the color blocks and match carefully
 - **Read** the pads in good light.
5. **Record** results on **PERL eCRF #8** and **Worksheet #08**.

Positive Multistix Results:

Below are some guidelines in the event of a positive Multistix finding:

***Leukocytes:** If positive for leukocytes, send sample to the lab for Urinalysis and culture. If urinalysis is abnormal, discuss results with the Study Physician.

***Nitrates:** If positive for nitrates, repeat the Multistix, being careful to follow the instructions exactly. If still positive, send sample to lab for Urinalysis. If abnormal, request a culture and discuss the results with the Study Physician.

Urobilinogen: If positive, confer with Study Physician.

Protein: If protein >30, but nitrates are negative, proceed as usual. If Nitrates are positive, see above.

- *Blood:** If positive, even at trace level, send Urinalysis to lab and discuss with Study Physician as to how to proceed.
- Ketones:** If positive for ketones, check BG and Study Physician for further instructions.
- Bilirubin:** If present for bilirubin, confer with Study Physician.
- Glucose:** If glucose >250, confer with Study Physician.

NOTE:

- Please note that trace and/or small results is a positive finding
- If the Multistix purchased at your site does not contain Bilirubin or Urobilinogen, indicate as "not tested" on the Multistix Worksheet #8.

***IMPORTANT:** HOLD iGFR procedure in the presence of leukocytes, nitrates, blood, or symptoms of UTI. (See Section 4.5.3.1.)

Positive Urine Culture:

If a participant has a positive urine culture, the urine samples for protein and bio repository should wait to be collected. A repeat urine culture should be collected once antibiotics are completed and the urine samples for protein and bio-repository should wait until there is a negative urine culture at least 48 hours after antibiotics are discontinued.

In the case of positive results requiring a Urinalysis/Urine Culture, the clinical center may use their own clinical judgement as to whether to send the participant to the local lab or refer them to their PCP for diagnosis and treatment.

4.2.3. Storage of Multistix:

All unused strips must remain in the *original* bottle. Transfer to any other container may cause reagent strips to deteriorate and become unreactive. Store at temperatures between 15°-30°C (59°-86°F). Do not use the strips after their expiration date. Do not store the bottle in direct sunlight and do not remove the desiccant from the bottle.

IMPORTANT NOTE: Protection against exposure to light, heat and ambient moisture is mandatory to guard against altered reagent reactivity.

4.3 Pregnancy Testing:

Experience with allopurinol during human pregnancy is limited because women of reproductive age rarely require this treatment. Given this paucity of data, the study will consider it unsafe for the fetus or the mother to receive this drug. Allopurinol has been found in the milk of a mother of this drug and, therefore, will not be taken by nursing mothers.

Regular pregnancy tests and education regarding fetal risk of the study drug will be provided to female patients of childbearing age.

To avoid fetal risks from the study drug, women who are breast-feeding, pregnant, or wanting to become pregnant during the next three years, may not participate in this study. Women who have not undergone hysterectomy, tubal ligation, or have not undergone menopause (LMP >1yr.) must use an acceptable birth control method to prevent pregnancy, such as systemic hormones (birth control pills, implant), intrauterine device (IUD), or a barrier method (male or female condom, diaphragm with intrauterine spermicide, cervical cap).

Sexually active female patients should be instructed to notify the study investigator or study staff immediately, if they become pregnant, suspect they might be, or stop their current method of birth control. They should also discontinue study drug and RAS blockers if a menstrual period is missed by more than two weeks and until a pregnancy test has been performed. If the test is positive for pregnancy, the study drug AND RAS blockers should **not be resumed until pregnancy and nursing are completed**. Pregnant/nursing mothers will continue to participate in the study visits (with the exception of the iGFR procedure). The study investigator and/or study staff will follow the progress of the pregnancy and birth of the baby.

Pregnancy tests will be done on all women of childbearing potential **at each visit**. Women, who are *not* of childbearing potential, will be identified as having:

- Hysterectomy
- Tubal Ligation
- Post-menopausal (defined at >1 year since last menses)
- Oophorectomy
- Other

Indicate on the Demographic Worksheet #2 the date of last menstrual period (LMP), as well as the date of surgery, if applicable.

Serum pregnancy testing will be performed at ALL PERL study visits. In addition, **BOTH** a serum **AND** urine pregnancy test will also be performed prior to the iGFR procedure (V4, V11, V15, V16), in order to have an immediate result prior to beginning the procedure. The procedure for urine pregnancy dipstix is described below.

Male Patients:

There are no data to support the risk of fetal malformations if a father takes allopurinol, thus there is no evidence to support warning to male participants.

4.3.1. Urine Pregnancy Dipstix: QuickVue One-Step* hCG Urine test is a one-step immunoassay intended for the qualitative detection of human Chorionic Gonadotropin (hCG) in urine for the early detection of pregnancy. hCG is a hormone produced by the placenta shortly after implantation. Since hCG is present in the urine of pregnancy women, it is an excellent marker for confirming pregnancy. * *If your site prefers a different Urine Pregnancy DipStix, please refer to the package insert for instructions.*

Urine pregnancy dipstix should be performed on all women of childbearing potential at V2, V4, (V4a if applicable), V11, V16, and V17, the latter four to rapidly determine if the participant can proceed with the iGFR (see below) (a serum pregnancy test is still performed as part of the local safety labs as at all other visit)

4.3.2. Specimen Collection and Storage:

Collect urine specimens in clean containers. First morning specimens generally contain the highest concentrations of hCG and are recommended for early detection of pregnancy. However, any urine specimen is suitable for testing.

Specimens may be kept at room temperature for 8 hours, or refrigerated at 36^o-46^oF (2-8^oC) for up to 72 hours.

4.3.3. Test Procedure:

1. Remove the QuickVue Test Cassette from the foil pouch just before use and place it on a clean, dry, level surface.
2. Using one of the disposable pipettes supplies, collect sample and add **3 DROPS** of urine to the Round Sample Well on the Test Cassette. The Test Cassette should not be handled or moved until the test is complete and ready for reading.
3. **WAIT THREE MINUTES AND READ**
4. **Positive:** Any pink-to-red Test Line (T) along with a blue Control Line © is a positive result for the detection of hCG.
5. **Negative:** A blue Control Line © and no pink Test Line (T) is a negative result.
6. **Invalid Result:** The test result is invalid if a blue Control Line © is not visible at 3 minutes. If this happens, retest using a new sample and a new Test Cassette.
7. Record results on the Local Lab Results eCRF and Worksheet #08.

NOTE: If a urine pregnancy test is questionable or positive, send STAT serum hCG test to local lab for quantitative hCG. If participant is already randomized and taking study medication, the medication should be STOPPED and the iGFR procedure should NOT be performed until a negative result is confirmed.

4.4. ECG

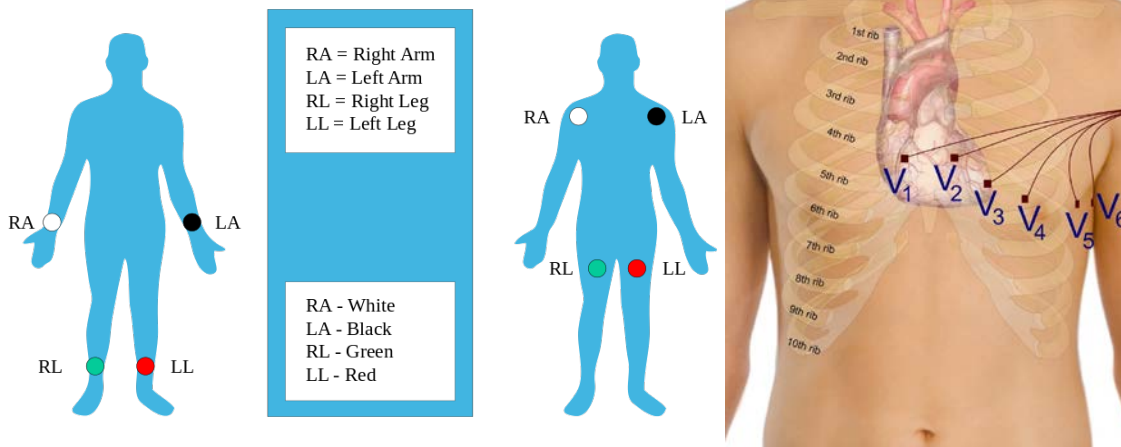
The 12 lead electrocardiograms (ECG) shows the electrical activity occurring in the patient's heart at the moment it is recorded. It is an important diagnostic investigation of arrhythmia's (i.e.) atrial fibrillation, or more serious conditions, such as myocardial infarction or cardiac arrest.

For the PERL Trial, an ECG is performed at Visits 2 (for subjects that do NOT skip the Run-In period), 4, 4a, 11 and 16.

The following are general guidelines in performing an ECG. Please refer to your Institutional protocol/procedure manual for more detailed information on the ECG model type your site is using.

Steps to Perform an ECG:

- Gather Equipment: Hand sanitizer, ECG machine, 10 sticky pads for attaching electrodes to, a razor (if applicable), and extra wipes or towel.
- Wash your hands and introduce yourself to the patient, and clarify their identity.
- Explain what you are going to do, and obtain consent to proceed. Clarify why the test is being performed.
- Ensure the participant is comfortable. For female participant's, be sure to ask them if they would like a female staff member to perform the ECG. If not, offer a chaperone to be in the room.
- For the ECG pads to stick properly there MUST be good contact with the skin. You may need to shave hair, or remove any cream or lotion that was supplied to the skin.
- Input the participant's data into the machine (according to Institutional protocol), to ensure that the correct details are printed on the ECG tracing.
- Attached the sticky pads (4 limb leads, and 6 chest leads). Place on the skin as follows:
 - Right wrist (or shoulder)
 - Left wrist (or shoulder)
 - Right ankle (laterally)
 - Left ankle (laterally)
 - V1 in 4th intercostal space at the right sternal edge
 - V2 in 4th intercostal space at the left sternal edge
 - V3 between V2 and V4
 - V4 in 5th intercostal space in the mid-clavicular line
 - V5 horizontal to V4 in anterior axillary line
 - V6 horizontal to V4 and V5 in mid-axillary line



- Attach the leads to the pads
The limb leads are colored red, yellow, green and black.
 - Black- Left arm
 - White – Right arm
 - Red – Left leg
 - Green – Right leg
 - The chest leads are usually numbered V1-V6 as shown.
- Once all the leads are attached, ask the participant to lie as still as possible. Record the reading and print a copy.
- Disconnect the leads from the pads and allow the participant to remove the pads themselves, or offer assistance if needed. Offer a wipe and dry towel for the participant to remove the sticky coating.
- Allow the participant to dress.

The ECG tracing is your source document. It must be reviewed by the Study physician as being read, signed and dated by him/her.

Complete eCRF #09 in OpenClinica, indicating date of ECG, heart rate, findings: normal/abnormal. If abnormal, indicate: ST elevation, atrial fibrillation, T wave inversion, Q waves, AV block, MI changes, tachycardia, bradycardia, or other. Indicate if the abnormality is clinically significant. If so, report on AE Log #20. Upload ECG to OpenClinica.

NOTE: If abnormal findings are shown on the ECG, previous ECG records should be sought for reading comparison. Participants should be referred to their primary physician for evaluation of ECG changes, or the Emergency Department for acute changes.

4.5 Glomerular Filtration Rate (iGFR)

One of the most cumbersome, and yet most vital, tests that the PERL participants will be asked to perform is the Iohexol Glomerular Filtration rate test (iGFR). This test takes approximately 5 hours, but fortunately is performed only 4 times during the 3 ½ years of the study. It is important to explain how important this test is in determining kidney function, that it is a test that is NOT done as part of their routine care at their personal physician's office, and that the risks are VERY low. Participants will hopefully accept it as a personal benefit for evaluating how well their kidneys are functioning.

In PERL, we will be measuring the patient's GFR as determined by the plasma clearance of non-radioactive iohexol (Omnipaque). Iohexol is a colorless to pale yellow iodine solution. Following injection of iohexol, timed measurements will be taken, to determine the rate at which the iohexol is excreted by the kidneys. A delay in excretion is an indication of renal impairment.



All centers will be provided with iohexol preparation Omnipaque (300mg iodine/ml containing Iohexol (3.235 gm) (GE Healthcare, NDC 0407-1413-10). Each single-dose vial contains 10 ml. (See Appendix for Omnipaque package insert). Omnipaque should be protected from light if removed from carton, and should be stored at 68° – 77°F (20°-25°C). Do not freeze.

The iGFR procedure will be performed at Visit 4, Visit 11, Visit 16 and Visit 17.

The participant should be instructed on the the iGFR preparation as indicated below. Participant's should also be provided with written instructions and be encouraged to ask questions about the procedure. Patient Instructions are located in the Appendix.

4.5.1. Instructions to Participant

Participant should be instructed on the following items prior to the iGFR:

1. Discontinue Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), e.g. Advil, Motrin, Aleve, ibuprofen) for 3 days prior to the iGFR. Tylenol and Aspirin are OK.
2. Follow a low-protein diet (no large portions of meat) for 24 hours prior to the iGFR.
3. Avoid strenuous exercise for the 24 hours prior to the iGFR.
4. If possible, ask participant to come in fasting. Participant should be well hydrated by drinking WATER ONLY prior to the iGFR.
5. Participant **should take morning medications and long-acting insulin the morning of the procedure, prior to coming to their appointment.** If they are using an insulin pump, they should leave the basal rate running. Short-acting insulin should be injected at the study clinical site before breakfast.
6. Instruct patient/participant to set a blood glucose (BG) *goal* of 90-160 mg/dL the morning of the visit (90-199 mg/dL is acceptable). If the BG is <100 mg/dL they should have ½ cup

orange juice or 3 glucose tablets and check to be sure the BG is above >100 mg/dL before driving.

7. Verify that the patient/participant is not allergic to iodine-based contrast media. **A seafood allergy is not exclusionary.**
8. The participant should be told that the procedure takes approximately 5 hours total.

NOTE: Use iGFR Nursing Worksheet #18 to document the procedure. The Nursing Iohexol iGFR Worksheet #18 is a **REQUIRED source document**, which **MUST** be completed in its entirety and uploaded to OpenClinica for remote monitoring.

4.5.2. Prior to the iGFR

- Verify Informed Consent has been signed
- Confirm date/time of last food/drink. Indicate if lab tests were performed fasting.
- Confirm low protein diet and no strenuous exercise for 24 hours prior to iGFR.
- Confirm no NSAID's for 3 days prior to iGFR. (Use of Tylenol and Aspirin OK)
- Verify that the participant is not allergic to iodine-based contrast media. **NOTE: A seafood allergy is NOT exclusionary.**
- Record the date and time of last medications (including insulin)
- Measure vital signs, height (in cm) and weight (in kg). Use BMI calculator for calculating BMI. www.nhlbi.nih.gov/guidelines/obesity/BMI/bmical.htm

4.5.3. To Be completed BEFORE iGFR Start:

4.5.3.1. Urine Multistix (See Section 4.2): Clean catch urine sample morning of visit for urine chemistry with Multistix. Record results on Nursing Iohexol iGFR Worksheet #18 as positive/negative for nitrates, blood, ketones and leukocytes. Indicate if ketones are negative/positive: small/moderate/large.

NOTE: HOLD iGFR in the presence of leukocytes, nitrates, blood, or symptoms of UTI. Request stat urinalysis to confirm. In the absence of fever or other symptoms, *i.e.*, back pain, abdominal pain, you may proceed with the iGFR after conferring with the Study Physician. If positive or the participant has symptoms, *i.e.*, dysuria, increased frequency, refer participant to PCP for treatment. Delay iGFR until **at least one week** after successful completion of therapy. If the participant has medical insurance, they may have this testing done at their personal physician's office and their records sent to the Clinical Center.

4.5.3.2. Pregnancy Testing (See Section 4.3): Perform urine pregnancy test (HCG) for all females of childbearing age and record results on the Nursing Iohexol iGFR Worksheet #18.

If urine pregnancy test is questionable or positive, send **STAT** serum HCG test to local lab for Quantitative HCG, stop study meds, and hold initiation of iGFR until **serum negative** result is confirmed. Study meds may be resumed if pregnancy test is negative.

4.5.3.3 BP Measurements (See Section 4.6): Obtain (3) BP readings, after participant is able to sit for at least 5 minutes, with both feet flat on the floor. Obtain readings from **RIGHT ARM**, unless contraindicated. Record results on Nursing Iohexol iGFR Worksheet #18.

4.5.3.4. Calculating the Mean BP: Calculate the Mean SBP by adding Systolic BP of #2 and #3, and divide total by 2. Calculate the Mean DBP by adding the Diastolic BP of #2 and #3, and divide by 2.*

*** If the Mean SBP readings of #2 and #3 is >150mmHg OR the Mean DBP readings of #2 and #3 is >95mmHg at Visit 4, the iGFR should be postponed, as this, if confirmed, is an exclusion criterion. The iGFR may be rescheduled for V4a, after conferring with the Study Physician. If the BP remains elevated at V4a, the participant should NOT proceed with the iGFR or with V5. The participant's personal physician should be notified of the elevated blood pressure for consideration of treatment. If at some point in the near future there is reason to believe the patient may be normotensive, rescreening could be considered. (Refer to Rescreen Section 2.4 of the MOO for detailed information).**

4.5.3.5. IV Insertion: If the participant has met BP (at V4/4A) and urine chemistry criteria (as above), insert IV into each arm,* using a #20 or #21 gauge angiocatheter—one for administration of Omnipaque and insulin (as needed) and the other for blood sampling. Allow 15 minutes for vein stabilization. A saline lock may be used for both IV sites.*

*If unable to start a second IV, the initial IV may be used for administration of Omnipaque, and for the collection of blood samples; however, the catheter **must be flushed thoroughly with Normal Saline** (5X the volume of the tube distal to the point of medication administration) **with each blood draw, followed by a Normal Saline drip at a rate of 20-30 ml/hour.** Document on Nursing Iohexol iGFR Worksheet #18 IV site #1 and #2.

4.5.3.6. Baseline Blood Draws: Draw CBL baseline bloods (3) 10ml red-top w/gel separator tubes; (3) 10ml EDTA purple top tubes, in addition to local lab samples. Obtain 1ml of venous blood to test BG using YSI **or** blood glucose meter* to determine if subject is eligible to proceed with iGFR. Record result on Nursing Iohexol iGFR Worksheet #18.

IMPORTANT: If patient arrives fasting, baseline bloods should be collected before breakfast and before the administration of glucose or insulin to bring BG in the desire range. Baseline bloods should also be drawn prior to performing the iGFR procedure.

***NOTE:** If using BG meter, it must be re-calibrated upon opening a new bottle of blood glucose strips.

4.5.4. BG Goals PRIOR to the iGFR: Target BG 90-199mg/dL

Before breakfast and AM insulin, check BG. Use these corrections if hyperglycemia or hypoglycemia is present (BG \geq 200 mg/dL or $<$ 90 mg/dL): (Call study physician if unsure as to how to proceed).

- **If BG is 90-199 mg/dL** (Target Range) have participant take their own usual a.m. insulin SQ, and provide them with breakfast (if desired) of no more than 45-60 carbohydrates). If participant does NOT eat breakfast, instruct them to take their long acting insulin (if they have not already done so), and adjust the fast-acting insulin based on their current BG.
- **If BG is <90 mg/dL:** Give participant 3 glucose tablets, or 4 oz. orange juice immediately, followed by breakfast of 45-60 gm CHO. If BG is $<$ 50mg/dL, and patient is **symptomatic**, give 30 gm fast acting CHO, followed by breakfast of 45-60 gm CHO. Consult with Study Physician as to whether or not to proceed. Have participant take usual AM insulin SQ **AFTER** they have started eating, using insulin-to-carb ratio to cover CHO consumption, adjusting for lower BG. Check BG in 15 minutes. If BG is \geq 90-199mg/dL, continue on with iGFR.

- **If BG is ≥ 200 mg/dL:** *HOLD* breakfast, and delay iGFR until BG is < 200 mg/dL. Check urine for ketones.
 - **If BG is ≥ 200 mg/dL** and ketones are **moderate or large**, hold breakfast and delay GFR until BG is < 200 mg/dL. Give patient short-acting Regular Insulin (Humulin R or Novolin R) as **IV Bolus of .08 u/kg over 1 minute**. Recheck BG every 15 minutes until it is in the target range. If BG is not dropping within 30 minutes, repeat the IV bolus and check BG in 15 minutes. When BG is < 200 mg/dL, have participant take AM insulin SQ (participant's usual dose, but reduce fast acting insulin by same amount given IV), breakfast (if desired), and proceed with iGFR. DO NOT bolus insulin sooner than 30 minutes after previous bolus.
 - **If BG is ≥ 200 mg/dL** and ketones are **negative**, hold breakfast and delay GFR until BG is < 200 . Give patient short-acting Regular insulin (Humulin R or Novolin R) as **IV Bolus of .05 u/ kg** over 1 minute. Recheck BG every 15 minutes until it is in the target range. If BG is not dropping within 30 minutes repeat the IV bolus and check BG in 15 minutes. When BG is < 200 mg/dL, have participant take AM insulin SQ (participant's usual dose—reduce short acting insulin by same amount given IV), breakfast (if desired) and proceed with iGFR. DO NOT bolus insulin sooner than 30 minutes after previous bolus.

4.5.5. Matrix to maintain BG DURING the iGFR: **Target Goal 90-160 mg/dL**

The **goal** is to maintain blood glucose in the 90 to 160 mg/dL range during the iGFR, however up to 199mg/dL is acceptable. Treatment for **hyperglycemia** will be initiated if the BG reaches ≥ 200 mg/dL, or **hypoglycemia** of < 90 mg/dL.

- **If the BG falls to < 90 mg/dL** give participant 3 glucose tablets or 4 oz. of orange juice (15 gm CHO) and re-check BG in 15 minutes. If BG is < 50 mg/dL, and patient is *symptomatic*, give patient 20-30 gm fast acting CHO, followed by one-half sandwich and 8 oz. of milk. Consult with Study Physician on how to proceed.
- If **BG is ≥ 200 mg/dL** check urine for ketones.
- If ketones are **moderate or large** give participant short-acting Regular insulin (Humulin R or Novolin R) as **IV Bolus of .08 u/kg over 1 minute**. Monitor BG every 15 minutes until it is in the target range. Do not bolus insulin sooner than 30 min. after previous bolus.
- If ketones are **negative** give participant short-acting Regular insulin (Humulin R or Novolin R) as IV Bolus of **.05 u/kg** over 1 minute, and monitor BG every 15 minutes until it is in the target range. Do not bolus insulin sooner than 30 min. after previous bolus.
- **NOTE: DO NOT give IV insulin for at least 1 hour after participant administers his/her own insulin subcutaneously.**

4.5.6. Additional Instructions

Participants using an insulin pump should be instructed to leave it running at usual basal rate during the iGFR. Participants using injections should take their long-acting insulin in the AM. This may be done at home prior to coming for the iGFR appointment.

- Participants should be offered a standardized low-carb snack 2 hours following breakfast (30 gm CHO), and a standardized low carb lunch (no more than 60 gm CHO) 2 hours after the mid-morning snack during the iGFR. Participants should take their own insulin SQ prior to lunch, and continue to test BG every 15 minutes.
- **INSULIN** for IV boluses will be provided by the Clinical Research Center and should be used if the participant is above target range. Do NOT use the participant's insulin.
- Refer to Study Physician when in question
- **Participants should NOT consume caffeine, carbonated beverages, or concentrated carbohydrates during the iGFR.**
- Participants should have minimal activity with bathroom privileges during the iGFR. Position should remain *consistent* for the duration of the iGFR to avoid postural changes on the iGFR. *Recumbent* is preferred position, but sitting in a comfortable chair is an acceptable option that the participant may prefer. Participant's should use washroom shortly *after* blood draws, thus avoiding postural influences on the iGFR.

4.5.7. Preparing for the iGFR: (Note: A copy of the Omnipaque Package Insert is located in the Coordinator Drop Box for your reference).

1. Indicate the Lot and Expiration date of the Omnipaque on Nursing Iohexol iGFR Worksheet #18.
2. Indicate the Insulin type, lot and expiration date on the Nursing Iohexol iGFR Worksheet #18.
3. Clearly label sample tubes with the provided labels.
4. Fill a 10 ml syringe with *exactly* 5 ml of Omnipaque (300 mg iodine/ml), containing iohexol (3.235 gm). Discard leftover 5ml, unless you have another patient the same day. Omnipaque should be used **immediately** after drawing up into the syringe.
5. Weigh a filled syringe. Weigh syringe after injection. Determine the weight difference and record weight on the Nursing Iohexol iGFR Worksheet #18.
6. Inject Omnipaque into injection arm, **SLOWLY BUT WITHIN 2 MINUTES**. Ensure the entire dose is IV with no subcutaneous leakage. Flush the catheter with Normal Saline (equal to 5X the catheter length) (from end of syringe to distal end of the insertion site into the vein).
7. Following injection, note the **exact** time that the injection is completed and start the clock. **Zero "0" time** is the time the injection is **FINISHED**. Use the same clock for timing throughout the procedure.
8. Collect blood samples at \pm 15 seconds of **120, 150, 180, 210 and 240** minutes after iohexol injection. Withdraw blood volumes at least equivalent to the cannula volume (1.5 ml) PRIOR to blood sample, to avoid dilution with saline. Discard as waste. Draw blood samples of 4ml each from the *sampling arm* into green heparinized tubes, noting **EXACT** time sample *should* be drawn, as well as the exact time the samples *are* drawn on the Nursing Iohexol iGFR Worksheet #18. If timing is different from the goal, continue with blood draws using the "zero" time as the proper interval. Be careful not to dilute the sample with saline.

9. Following completion of the iGFR, remove IV's. Encourage increased fluids for remainder of day to flush Iohexol from system.

NOTE: Observe for signs of allergic reaction and remain with participant for one hour after injection. Common side effects include: warm feeling in face, bitter/metallic taste in mouth minutes after injection.

4.5.8. Emergency Treatment for Anaphylactic Reaction:

Adverse reactions following the use of Omnipaque are usually of mild to moderate severity. However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin have been associated with iodine-containing contrast media, including Omnipaque. The injection of contrast media is frequently associated with the sensation of warmth and pain. Most adverse reactions to injectable contrast media appear within 1-3 minutes after the start of the injection, however delayed reactions may occur. *(Please refer to the Omnipaque package insert for detailed information regarding adverse reactions.)*

All sites performing iGFR procedures should have *immediate* access to Emergency treatment on the unit. In the event of an anaphylactic reaction, please follow the following procedures *(as outlined in the iGFR Physician orders)*:

- Call emergency assistance or 911
- Determine subject's **level of responsiveness**
- Position subject **supine** (face up), and flat on a hard surface if unresponsive. Use cardiac board if needed
- Discontinue all IV **Medications** immediately. Withdraw blood from IV to remove residual medications. FLUSH IV line with Normal Saline. Leave IV intact with Normal Saline running at a rate of 20-30 ml/hr, or higher if needed for BP support, as directed by Study Physician.
- Initiate basic cardiac life support (BCLS)
 - a. Assess airway
 - b. Assess breathing
 - c. Assess circulation
- Obtain emergency supplies and equipment, such as Automatic External Defibrillator (AED), Crash Cart, and Emergency Kit.
- If subject is unresponsive, immediately apply AED, and follow prompts.
- Notify Study Director and Study Physician STAT
- If anaphylaxis is suspected (i.e. symptoms involving 2 or more organ systems)
 - a. Administer **Epinephrine 1:1000 via EpiPen** intramuscularly into thigh muscle. *(If thigh muscle is problematic, epinephrine can be administered in the deltoid muscle.)* DO NOT DELAY administering EpiPen, as this is life-saving in an anaphylactic reaction.
 - b. If there is good response, observe subject.
 - c. If no response, or poor response, **REPEAT** EpiPen, every 10-15 minutes, up to a MAXIMUM of 3 doses.
 - d. For treatment of symptoms such as pruritus, erythemas, or urticaria, administer **Diphenhydramine (Benadryl) 50 mg/ml** Intramuscularly (IM) **ONCE**. Diphenhydramine should **NOT** be repeated.
 - e. Administer oxygen by mask or nasal cannula as indicated.

- f. If subject is on chronic Beta-Blocker therapy and has signs of clinical worsening, check BG for hypoglycemia. Consider **Glucagon 1.0 mg intramuscularly** if unable to check glucose, or subject's condition nor improving or worsening.
- g. Place subject in **recumbent position** with lower extremities elevated, unless in respiratory distress.
- h. Obtain and monitor **vital signs** every 2-5 minutes—remain with the subject until he/she is transported to an emergency department.
- i. Document event and all interventions/medications administered on the **ASSESSMENT GUIDE AND RECORD** attached to the iGFR Physician orders.

4.5.9. Preparing Samples for Measurement:

- 1) Fill labeled tube completely with blood. Invert tube 8 times. Centrifuge each timed tube as they are collected, OR hold them at room temperature and centrifuge all 5 tubes together. Centrifuge for 10 minutes at 3000 x g. Proceed to specimen aliquot procedure.
- 2) Using a plastic transfer pipet, remove the clear plasma supernatant and distribute the plasma evenly into each of two pre-labeled 2.0 ml microvials. Aspirate slowly starting at the top of the plasma. Do not disturb the white blood cells layer, also called the buffy coat, which forms a thin layer between the upper plasma layer and the lower layer of packed red blood cells. Leave ¼ - ½ inch of plasma on top of the undisturbed buffy coat. Fasten green o-ring screw caps onto these vials. One vial for each timed collection is shipped to the Central Lab, and the second to be stored as a backup at the Clinical Center.
- 3) Bundle each subject's specimens together (two bundles of five tubes each), place in Ziploc bags, place upright on rack and freeze at -70°C. Store one set at -70°C until ready to ship to the Central Biochemistry Laboratory (CBL). Store the second (backup) set at the clinical site at -70°C until official confirmation of a valid iGFR procedure is received from the DCC, after which this set of samples may be discarded. **NOTE:** If you will be shipping same day, samples must be frozen at least 30 minutes prior to packing.

To package specimens for shipment, place the Ziploc bag containing 5 iGFR specimens into one side of a compartmentalized freezer box on a layer of **dry ice**. **The iGFR specimens must be kept frozen at all times.** Be sure to use sufficient dry ice. The amount of dry ice should total at least 5 pounds (10 pounds) for International shipments. (See Section 5 of the *Central Laboratory Biospecimen Collection and Processing Manual* for detailed information).

- 5) Once the shipment is complete, place the lid on the freezer box and place the PERL Shipping Form (#37) on top. Close the flaps on the cardboard sleeve and seal the box. For **Visit 4**, samples are shipped twice per week, on **Monday and Wednesday**. For iGFR **Visit 11, 15, 16**, samples are shipped on the **first Monday of the month**.

5. Use Federal Express Overnight courier service to ship samples to the CBL. Shipping address:

Naomi Thompson/ PERL Central Biochemistry Laboratory
University of Minnesota
Advanced Research and Diagnostic Lab (ADRL)
1200 Washington Ave, South, Suite 175
Minneapolis, MN 55415
Telephone: (612) 625-5040
Fax: (612) 273-3489

NOTE: Send an email to notify Anna Lukkari: lukka019@umn.edu; Van Le: lex557@umn.edu and Naomi Thompson: thom4228@umn.edu that a shipment was sent.

8) The CBL will send raw data on participants to the Data Center (DCC). The DCC will perform calculations on the raw data.

NOTE: A valid iGFR result is needed PRIOR to randomization. The DCC will notify the site once the participant is cleared for randomization via email. **DO NOT** randomize the participant until you have received notification of a valid iGFR.

4.5.10. Abnormal GFR'S

NOTE: If there is a $\geq 50\%$ reduction in GFR in one year, confirmed by doubling of serum creatinine in one year, the Clinical Center will be notified and a DMC meeting/conference call is required.

4.5.11 Calculations

Iohexol clearance will be first calculated according to a one-compartment model (CL1) by the formula:

$$CL1 = \text{injected dose of iohexol/AUC.}$$

(AUC: area under the curve of the plasma concentration of iohexol)

The value is then corrected according to Brochner-Mortensen (Scand. J. Clin. Lab. Invest 30:271-274, 1971), to estimate GFR (plasma clearance) by using the formula:

$$GFR = (0.990778 \times CL1) - (0.001218 \times CL1^2)$$

GFR value then will be normalized by the body surface area ($GFR/1.73m^2$). If the Body Surface Area is less than $1.73m^2$ it is adjusted (standard score); if it is $>1.73m^2$, the raw score is used.

4.5.12. GFR Processing Instructions

Iohexol Assay:

Iohexol plasma concentrations are determined by HPLC using a method based on that of Krutzen, et al, J. Lab. Clin. Med. 104: 955-961, 1984.

4.6. Blood Pressure (BP) Procedure

Blood pressure eligibility criteria are assessed at the screening visit (Visit 1) and at the end of the Run-In period (Visit 4). If the BP criteria are not met at Visit 1 ($SBP \leq 160$ and $DBP \leq 100$ mmHg), the patient will be referred to their primary physician for blood pressure management. The patient may then be re-screened **two** additional times at least 4 weeks and no later than 6 months after the Visit 1 assessment. If the BP limits are not met at Visit 4 ($SBP \leq 150$ and $DBP \leq 95$ mmHg), then the patient may be re-assessed at Visit 4A, two weeks after the Visit 4 assessment (See Section 8.3 of the Protocol). If the BP is not $\leq 150/95$ mm/Hg at visit 4A, the participant will not be randomized into the study.

4.6.1. Clinical Center Blood Pressure Method

Blood pressure will be measured using a reliable blood pressure monitor that is calibrated every six months to one year. The correct cuff size is determined by measuring the circumference of the arm midway between the elbow and shoulder. The cuff width should be equal to 80% of the circumference.

- 1) With participant seated, palpate the **right** brachial artery. Wrap cuff with the center of the bladder over the brachial pulse. Ensure that the bottom edge of the cuff is about 3.5 - 4.0 cms (\approx 2 inches) above the antecubital fossa. Cuff should be loose enough to permit the insertion of two fingers between the cuff and the arm. If the BP cannot be done on the right arm, you may use the left but this should be indicated at the front of the patient's chart.
- 2) Elevate the **right arm** to a level even with the heart. Have the participant rest quietly for five minutes before BP is measured. The legs should be uncrossed with feet flat on the floor and the participant should not speak while the BP's are being taken.
- 3) Monitor should be positioned to face away so that readings cannot be seen by the participant.
- 4) Take **three** blood pressure readings at 60 second intervals and record blood pressures, heart rate on eCRF #6. For analysis, only the second and third measurement will be used.
- 5) The BP goal for study patients (with or without medication) is $\leq 140/90$ mmHg. If the blood pressure is >140 systolic, or >90 diastolic, notify the study physician to determine if initiation or titration, using one or more of the following medications, is necessary.

NOTE: See "Other antihypertensive agents" below for further instructions if BP is $>140/90$.

Performing BP on the Left Arm:

There may be reasons for the left arm to be used for blood pressure measurement, instead of the right (i.e. patient preference, axillary lymph node dissection, etc...). Noting this and the reason should be documented as a Protocol deviation. Sites should complete the protocol deviation Worksheet# 40 and enter into OpenClinica. (eCRF # 40) **NOTE:** ALL "home" and clinical center blood pressures should be CONSISTENTLY done on the **same** arm.

Remote Blood Pressure Measurement:

The following procedures should be followed for remote visits:

- If the remote visit is for VISIT 1, the patient will also need to go to their PCP office for BP measurement (per PERL protocol). Since we need to determine if BP at Visit 1 meets eligibility criteria, it will be important to have an accurate measurement.

- For all other remote visits, participants will perform their BP at home, using their BP monitors and forward the results to the Coordinator. After the Coordinator reviews the readings, if they are out of range, the Coordinator needs to refer the patient to the site or their PCP for confirmation.
- Patients should bring their BP monitor to all Main site visits, to compare against the calibrated BP monitor at the site.

4.6.2. Effects of RAS blocking (RASB) therapy on BP

Letters will be written to the participants' physicians informing them about the study and notifying them of the study's protocol RASB requirements and blood pressure goals. The letter will propose active participation of the participant's physicians in blood pressure management with the availability of advice from the PERL site physicians and, if needed, the PERL Drug Monitoring Committee for out of range blood pressure values during the course of the study. The Run-In period will start at **Visit 2**.

If the participant is already on an RAS Blocker, its dose will be increased, if necessary, to make it at least equivalent to Ramipril 10mg (if on ACE inhibitor [ACEi] or Irbesartan 300 mg [if on an angiotensin receptor blocker [ARB]], if acceptable to the participant's primary physician, if tolerated, and if not contraindicated.

Participants who were not taking an RAS Blocker will be prescribed and instructed to start taking 10mg of Ramipril daily, or 300 mg of Irbesartan daily (if Ramipril is contraindicated or the participant has side effects), or another ACE inhibitor or ARB at equivalent doses if there were impediments to the use of Ramipril or Irbesartan.

Participants who have contraindications to RASB (e.g. SBP <100mmHg, K⁺ >5.5mEq) or do not have evidence or history of micro or macroalbuminuria (as defined in 5.1.4 of the Protocol), are normotensive, and are not being treated with RAS Blockers or other anti-hypertensive agents will not be treated with these drugs, as this represents the standard of care.

NOTE: Participants who are started for the first time on RAS Blockers as part of this study will start at half a dose: if there are no side effects, this will be increased to a full dose at Visit 3 and their serum K⁺ and creatinine measured at a local laboratory after two weeks. (See section 8.3 and 9.4 of Protocol). This will be paid for by the PERL study.

RAS Blockers will be immediately discontinued in the case of allergic reactions, or angioedema or the suspicion of pregnancy. If pregnancy is confirmed, the patient will remain off RAS Blockade until the pregnancy and breast-feeding are completed. If symptomatic hypotension (SBP <100 mmHg) or intractable cough develops in patients on ACEi their dose will be decreased to half, followed by their discontinuation. For persistent cough with Ramipril or other ACEi, Irbesartan or another ARB will be prescribed in place of the ACEi.

In the case of hyperkalemia (K⁺ ≥6mEq) or serum creatinine elevation (≥ 30% increase over baseline values), the participant will be asked to immediately obtain a confirmatory lab value at their local lab or clinical site, and then discontinue the RAS Blocker while awaiting this confirmatory result. If confirmed, the participant will resume RAS Blockade **at half dose** 72 hours later, and will have **repeat labs one week later**. If the problem persists, RAS Blockade will be discontinued for the remainder of the trial and BP managed by alternate drugs (see below). If not confirmed, the participant will resume RAS Blockade at their usual dose and have a repeat lab check **one week later**. These same steps will be taken if hyperkalemia develops during the trial.

4.6.3. Other antihypertensive agents used to control BP

Participants will continue to take any other antihypertensive drug that they may have been taking before study entry. Participants will be provided with a blood pressure monitoring device (if they do not already have access to one), will be trained on its use, and will be instructed to periodically monitor their blood pressure at home and to record the results in a BP diary, and to communicate them to study personnel if values are abnormal.

If hypotension develops (SBP < 100 or significant lightheadedness), the dosage of non-RAS antagonist antihypertensive drugs will be progressively reduced until discontinuation or discontinued abruptly, followed by a reduction of RAS Blockers to half the dose and discontinuation if the problem persists.

If BP is found to be elevated (>140/90 mm Hg) on three consecutive occasions, the dose of existing non-RAS antagonists antihypertensive drugs will be maximized, followed, if necessary, by the introduction of antihypertensive drugs of a different class. These will be chosen in collaboration with the other health care providers that are involved in managing the participant's anti-hypertensive therapy. If the goal of BP \leq 140/90 is not achieved with these drugs within one month, a Drug Monitoring Committee conference call will be convened to consider the possibility of causes of hypertension other than diabetic nephropathy and discuss alternative therapeutic approaches. BP will continue to be monitored and the anti-hypertensive therapy to be adjusted in a similar way throughout the study.

NOTE: If BP \leq 150/95 mmHg is not achieved at Visit 4, the Run-In period may be extended for two more weeks after which the participants will be examined again as in Visit 4 (Visit 4a). In this event, the GFR measurement scheduled for Visit 4 will be conducted at Visit 4a. Participant's whose SBP is >150 mmHg or whose DBP >95 mmHg at the end of the Run-In period will be discontinued from the study (prior to randomization).

4.6.3.1.

Table 1. Approximate dose conversion for ACE inhibitors (from GRIPA 2006)

ACE Inhibitors

DRUG	LOW	MEDIUM	HIGH
Benazepril (Lotensin)	5 - 10 mg/day	20-40 mg/day	60-80 mg**
Captopril (Capoten)	6.25 mg TID	12.5-25 mg TID	37.5*-50 mg TID
Enalapril (Vasotec)	2.5 - 5 mg/day	10 – 20 mg/day	30* - 40** mg/day
Fosinopril (Monopril)	5 mg/day	10 – 20 mg/day	30* – 40 mg/day
Lisinopril(Prinivil,Zestrin)	2.5 – 5 mg/day	10 – 20 mg/day	30 – 40 mg/day
Moexipril (Univasc) ***	3.75* – 7.5 mg/day	11.25* – 15 mg/day	22.5 – 30 mg/day**
Perindopril (Aceon) ***	2 – 4 mg/day	6* – 8 mg/day	12 – 16 mg/day**
Quinapril (Accupril)	5 – 10 mg/day	20 – 40 mg/day	60 – 80 mg/day**
Ramipril (Atace)***	1.25 – 2.5 mg/day	5 – 10 mg/day	15-20 mg/day**

*Requires pill splitting of ACE inhibitors

** Requires multiple tablets (often less cost-effective)

*** Not available generically

4.6.3.2.

Table 2. Approximate dose conversion for ARB (from GRIPA 2006)

Angiotensin Receptor Blockers (ARB)

DRUG	LOW	MEDIUM	HIGH
Irbesartan (Avapro)	75 mg	150 mg	300 mg
Olmesartan (Benicar)**	<20 mg (5mg tabs available)	20 mg	40 mg
Candesartan (Atecand)	4-8 mg	16 mg	32 mg
Eprosartan (Teveten)	400 mg	600-800 mg	
Losartan (Cozaar)	25 mg	50-100 mg	
Telmisartan (Micardis)	20 mg	40 mg	80 mg
Valsartan (Diovan)	40-80 mg	80-160 mg	320 mg

**Olmesartan (Benicar) lowers the DBP & SBP approximately 3-4 mm/Hg More than the corresponding dose of the other ARB'S

Lowest dose of ARB's are often for patients with volume or salt depletion.

4.7 Skin Assessment

Prior to randomization, at Visit 4, participants will be tested for HLAB*58:01 genotype. Participants who are positive will be **ineligible** to participate in the study, as this would indicate an increased risk of Stevens-Johnson syndrome in response to allopurinol. Though only those participants with a negative HLAB*58:01 will be allowed to participate in the PERL study, it is very important that regular skin checks be performed. About 1-2 out of 100 individuals taking allopurinol experience some kind of skin reaction.

Stevens-Johnson syndrome is a rare, serious disorder of the skin and mucous membranes. It's usually a reaction to a medication or an infection. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then the top layer of the affected skin dies and sheds.

Stevens-Johnson syndrome is a medical emergency that usually requires hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications.

Participants should have a baseline skin assessment performed at their Physical Examination at Visit 4, as well as at Visits 6-15. Interim skin assessments should be performed by the participant at each visit as a "self-assessment," if these visits are conducted remotely, or by a member of the study staff if the visit is at the PERL site.

For self-skin assessment, participants should be instructed on how to perform the exam, as well as be reminded that it should be performed *prior* to their scheduled phone call with the site. The exam should be conducted in a well-lit room, in front of a full-length mirror. A hand held mirror can be used for hard to see areas. Participants may also seek assistance from a spouse or friend. All participants should be given a copy of the ***Self-Assessment Skin Exam for Rashes and/or Hives Instructions***, and should be asked to complete the ***Skin Assessment Worksheet # 11***, with the date of the exam and their signature, and return to the Study Coordinator if performing the self-examination.

Reporting of skin rash:

Patients should be instructed to notify study staff at the first signs of rash or hives. Participants should be asked questions such as:

- When did the rash first appear?
- Have they noticed any change in size or appearance?
- Are they having symptoms, such as itching, blistering, peeling, reddened areas, or areas of draining?
- Are they having more severe signs of allergic reaction, such as irritation of the eyes, swelling of the lips, mouth, tongue, or difficulty breathing?

In the event of rash, the Coordinator should confer with the Study Physician. Study medication will be **immediately** discontinued if symptoms and signs of skin reaction are present. If the skin rash is thought to be due to allopurinol, the participant will not resume the study medication.

NOTE: The risk of skin reaction is increased by the antibiotics Ampicillin and Amoxicillin.

4.8. Accurate Measurement of Height

Ask the participant to remove all footwear (shoes, slippers, sandals, etc) and head gear. (hat, cap, hair bows, comb, ribbons, etc) **Note:** If it would be insensitive to seek removal of a scarf or veil, the measurement may be taken over *light* fabric.

Ask the participant to stand with their back to the wall, feet together and heels against the Stadiometer, knees straight.

Ask the participant to look straight ahead and not to tilt their head up. Make sure the eyes are the same level as the ears.

Move the measure arm gently down onto the head of the participant and ask the participant to **stand tall**.

Have the participant move away from the Stadiometer while holding the measuring arm securely in place. Read the height in centimeters at the **exact point** and record the measurement on eCRF #06.

4.9. Accurate Measurement of Weight

Ask the participant to remove all footwear (shoes, sandals, etc), jacket or sweater, and any items in pockets which may contribute to additional weight.

When weighing the patient, it is preferred to:

- Weigh the patient at the same time of day
- Use the same scale
- Following voiding
- Before breakfast
- Have the patient wear the same type/amount of clothing

If using a digital scale for weight, calibrate to zero before participant steps on scale. Ask participant to step on scale and record weight. A second measurement assures the correct weight was measured.

Calculate BMI. Use BMI calculator for calculating BMI.

www.nhlbi.nih.gov/guidelines/obesity/BMI/bmical.htm

Document recorded weight in the patient's chart and on eCRF #06.

APPENDIX

4.10. FIRST VOID SPOT-URINE COLLECTION INSTRUCTIONS TO PARTICIPANTS

PLEASE NOTE THE FOLLOWING INSTRUCTIONS:

- ◆ Women: don't do the collection if you are menstruating.
- ◆ Don't do this collection if you are ill or if you have a urinary tract infection.
- ◆ Avoid strenuous exercise for at least 24 hours prior to the urine collection.
- ◆ Avoid the use of non-steroidal anti-inflammatory medications (Advil, Aleve, Motrin, etc.) for at least 48 hours prior to the urine collection.
- ◆ If you are instructed to do 2 collections, try to do them both as close to your clinic appointment as possible.

4.10.1. Collecting the Urine

- ◆ Open the *sterile* urine cup being careful not to touch the inside of the container or the inside of the lid.
- ◆ Using the towelettes provided for you, cleanse genitals (front to back) before beginning to urinate.
- ◆ Begin urinating in the toilet; after expelling a small amount of urine, catch a sample into the cup, filling it about one-half to three-quarters full.
- ◆ Put the cap back on the cup securing it tightly.
- ◆ Be sure your name and an ID number is on the label on the cup and write the date of the urine collection on the cup as well.
- ◆ The cup containing the specimen should be kept tightly closed and refrigerated or kept on ice until it is brought to the clinic.

4.11. INSTRUCTIONS TO PARTICIPANTS FOR OVERNIGHT URINE COLLECTION

PLEASE NOTE THE FOLLOWING INSTRUCTIONS:

- ◆ Don't do this collection if you are ill or if you have a urinary tract infection.
- ◆ Women: don't do the collection if you are menstruating.
- ◆ Avoid strenuous exercise for at least 24 hours prior to the urine collection.
- ◆ If you forget to put **ANY** urine in the container while doing the collection, empty the container, rinse it out with clean water, air dry, and start over another night.
- ◆ Avoid the use of non-steroidal anti-inflammatory medications (Advil, Aleve, Motrin, etc.) for at least 48 hours prior to the urine collection.
- ◆ The collections must be a **minimum of 4 hours** in duration.
- ◆ Maintain usual amount of liquid intake, but avoid alcoholic beverages.

If you have any questions, please call the study coordinator for clarification.

The goal of this collection is to collect **all** urine formed during a **carefully timed** period when you are **at rest**. Therefore, this collection needs to be done **the night before** and needs to be a **minimum of 4 hours** long. Do the collection **the night** before your appointment. **Keep the specimen refrigerated or on ice during the collection and during transport to the clinic.**

At Bedtime:

- ◆ Empty your bladder completely and **FLUSH** this urine.
- ◆ **THIS IS THE BEGIN TIME.**
- ◆ Write this exact "**BEGIN**" time on the jug labeled **OVERNIGHT URINE**.
- ◆ Drink a glass or two of water before you go to bed. (If your total collection is less than 150 ml, you will need to do it over another night).
- ◆ Save any urine you pass during the night and put it in the container.
- ◆ Empty your bladder on awakening and put this urine in the container.
- ◆ **THIS IS THE END TIME.**
- ◆ Write the exact "**END**" time on the container.
- ◆ This ends the overnight collection. Refrigerate or keep the specimen on ice until you bring it to the clinic.

REMINDER: BEGIN AND END THE COLLECTION WITH AN EMPTY BLADDER

- ◆ ***BEGIN TIME IS WHEN YOU EMPTY YOUR BLADDER AND FLUSH THE URINE.***
- ◆ ***END TIME IS WHEN YOU EMPTY YOUR BLADDER AND SAVE THE URINE.***

4.12. PATIENT INSTRUCTIONS FOR iGFR PROCEDURE

- If possible, come to your appointment fasting (nothing but water). You should take your morning medications and your long-acting insulin at home. If you are on an insulin pump you should leave the basal rate running. You will be instructed to leave your insulin pump running at the basal rate during the iGFR as well. Short-acting insulin will be injected at the clinical site right before breakfast.
- Discontinue Non-Steroidal Anti-Inflammatory Drugs (NSAIDS), (i.e.) Advil, Motrin, Aleve, ibuprophen 3 days prior to your appointment. This restriction does not include Aspirin or Tylenol.
- You will not be allowed to have the iGFR procedure if you have an allergy to iodine contrast media. *(Please note that a shellfish allergy is not exclusionary).* Please notify the study staff if you have had an allergy in the past to contrast media.
- Be sure to follow a low protein diet for **24 hours** prior to the iGFR (no large portions of meat)
- Avoid strenuous exercise for **24 hours** prior to the iGFR test
- DO NOT** consume caffeine, carbonated beverages or concentrated carbohydrates **before or during** the iGFR
- Please be well hydrated, by drinking **WATER ONLY** prior to the iGFR. You will also be encouraged to continue drinking water after the iGFR to flush the dye out of your system
- Please be sure to bring your overnight urine collection, with the date, and start and end times recorded
- You will be offered breakfast, a standardized low-carb snack mid-morning, and a standardized low-carb lunch during the iGFR.
- If you have been experiencing symptoms of a urinary tract infection (fever, cloudy or bloody urine, pain or burning on urination, pressure or cramping, abdominal or back pain), contact the PERL team before your appointment.
- If you have any questions regarding these instructions, please call:

[Study Coordinator] _____

Ph: _____

Email: _____

4.13. DOING BLOOD PRESSURE READINGS AT HOME:

When and how to check your BP's at home:

If your BP's are *higher* than 140/90 mmHg at a clinic visit, *or* if you begin taking a new study drug or BP medication, it is important that you check your BP's for the next few days to see the effect of the medication. The best time of day is shortly after waking up in the morning, before you've had coffee or eaten breakfast. However, by occasionally checking it later in the day you will also be able to see if your readings are consistent throughout the day. You should measure your BP once or twice weekly and record your readings on the Blood Pressure Log. *If at any time* your BP readings are lower than 100/60 mmHg, *or* if you are experiencing lightheadedness or dizziness, call your clinic nurse or coordinator as soon as you can to report the numbers.

If you are using your own BP monitor and it has not been calibrated with the PERL clinic monitor, you should take it with you to your next PERL clinic visit to check the accuracy. The BP monitor you are using at home should be accurate within 10 mm/Hg of the BP monitor used by the clinic. From then on you should take the monitor each time you go to the clinic for your half-day (kidney function) appointment (Visits 4, 11, 16, and 17). If you are using a BP monitor that the clinic provided, it is reliable and may be used right away, but this should also be taken to the clinic at the time of the GFR appointments for calibration.

- The BP's should be done on your *right arm*, unless you have been instructed to use your left arm. In that case you may use the left arm, but this should be indicated at the top of the BP log you are using to record the numbers.
- Connect the navy blue tubing to the blood pressure cuff and also to the white machine.
- Sit in a comfortable chair and place the center of the BP cuff about 2 inches (4 cms) above the bend in your arm, and lined up with the artery at the crease in your elbow. The cuff should be slightly snug but loose enough to permit the insertion of two fingers between the cuff and the arm.
- Elevate your arm to a level that is even with your heart by using a table or pillow. Rest quietly with your *legs uncrossed*, and *feet flat* on the floor before starting. Do not talk while the BP's are being taken.
- Press *Start* and wait for blood pressure cuff to inflate and give the reading. Take three blood pressure readings at 60 second intervals. Record the BP's, as well as the pulse results on the BP Log. Record the date, time, medications you are taking and notes that may have affected the readings, such as stress, illness, activity levels, hormonal changes, etc.
- If your BP readings are higher than 140/90 mm/Hg three times in a row, or lower than 100/60 mmHg call your clinic nurse or coordinator to report the numbers.

Note: The monitor can also store your readings and even be downloaded via additional cords/CD in the kit. Please read the additional instructions included in the monitor package if desired.

Remember to take your BP log to your next clinic appointment.

4.13.1. BP LOG

Any BP's that are done at home with the BP monitor provided by the clinic or your own, should be recorded on this for the RAS and BP Medication Log. If BP's are higher than 140/90 mmHg for 3 readings in a row you should call your clinical center to see if BP medication should be started or the dosage changed. If BP's are lower than 100/60 mmHg or if you are feeling light headed or dizzy, you should call your clinical center right away. If BP's are higher than 100/60 mmHG (and you are not having symptoms), and lower than 140/90 mmHG, it is not necessary to call the clinic, but you should take this log to the Clinical Center for your next visit.

<u>DATE</u> Mo/Day/Yr	<u>TIME</u>	<u>Systolic/Diastoli</u> <u>c BP</u>	<u>PULSE</u>	<u>CHANGE IN</u> <u>MEDICATION</u>	<u>NOTES</u>
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	
__/__/__	____am ____pm	____/____ mm/Hg	____ Beats/min	Med _____ Dose _____	

4.14. SELF-ASSESSMENT SKIN EXAM FOR RASHES AND/OR HIVES

Regular skin exams are especially important for participants in the PERL study because you are taking allopurinol, which puts you at a slight risk for a reaction. (About 1 or 2 individuals in 100 taking allopurinol experience some kind of skin reaction). Although you were screened for the HLA B*58:01 genotype (prior to randomization) which indicates an increased risk of Stevens-Johnson syndrome (a severe adverse reaction to a medication) in response to allopurinol, it is still very important that you do regular skin checks. Checking your own skin frequently, along with regular exams by the study doctor can help find rashes early, when they are easier to treat.

As part of a routine PERL 'in-clinic visit,' the study nurse or physician will check your skin carefully. During your physical exam, your nurse/doctor will note the size, shape, color, and texture of any area in question.

If you are doing a "phone visit" or "remote visit," it is important that you do a **self-skin assessment** *prior* to the phone call. The exam is best done in a well-lit room, in front of a full-length mirror. You should use a hand-held mirror to look at areas that are hard to see, such as your back and the backs of your thighs. A spouse or close friend or family member may be able to help you with these exams, especially for those hard-to-see areas like your back or scalp.

The first time you examine your skin, spend time carefully going over the entire surface. Learn the pattern of marks on your skin so that you'll notice any changes the next time you check. Be sure to call your PERL clinic to discuss any areas that concern you.

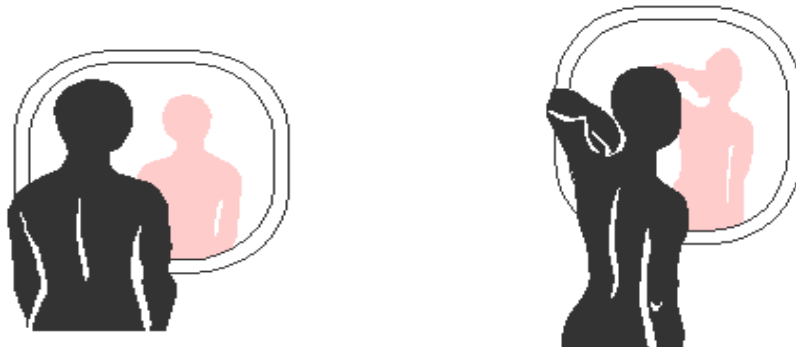
What you should look for:

Rashes and or hives can show up in many shapes and sizes. Be sure to talk to the PERL study staff about any areas that concern you, especially if they have just appeared or have changed recently.

Follow these step-by-step instructions to examine your skin:

Face the mirror:

- ◆ Check your face, ears, neck, chest, and belly. Women will need to lift their breasts to check the skin underneath. Check your underarm areas, both sides of your arms, the tops and palms of your hands and in between your fingers.



Sit down:

- ◆ Check the front of your thighs, shins, tops of your feet and in between your toes. Use a hand mirror to look at the bottoms of your feet, your calves, and the backs of your thighs, first checking one leg and then the other.



Use a hand mirror:

- ◆ Check your buttocks, genital area, lower and upper back, and the back of your neck and ears. It may be easier to look at your back in the wall mirror using a hand mirror.
- ◆ Use a comb to part your hair so that you can check your scalp.



The best time to do this simple exam is after a bath or shower. Check from the top of your head to your toes. If you look at your skin regularly you will know what's normal for you.

What to do if you find something suspicious:

If you develop any signs of a rash or hives you should call the PERL clinic staff right away to report it. Usually the first step is for the study coordinator to ask when the rash/hives first appeared, if they have changed in size or appearance, and if they're causing any symptoms such as **itching, pain, blistering, peeling, reddened areas, or areas of draining**. More severe signs of an allergic reaction include **irritation of the eyes, swelling of the lips, mouth, or tongue, or difficulty breathing**). The coordinator will then confer with the study physician. The study medication will be immediately discontinued if symptoms and signs of skin reactions are present. If the skin rash is thought to be due to allopurinol, you will not take this medication again.

NOTE: The risk of skin reaction is increased by the antibiotics **ampicillin and amoxicillin**. You should immediately inform the study personnel if you need to start these or other medications.

Chapter 5

Source Documentation and Monitoring

5.1. Goals of Monitoring

- Verify that subject consent for study participation has been properly obtained and documented, and that proper consent version(s) was used.
- Verify that research subjects entered into the study meet the inclusion and exclusion criteria.
- Verify that the study is conducted in compliance with the protocol.
- Ensure all reportable Adverse Events/SAEs are reported accurately and in a timely manner
- Verify the accuracy of the data collected.
- Verify study drug accountability and dispensing records.
- Verify that all regulatory and essential documentation required by good clinical practice guidelines are present, current and appropriately filed.

5.2. Methods of Monitoring in PERL

5.2.1 On-Site Monitor Visits

On-site monitor visits will occur at yearly intervals for the PERL study. A clinical monitor from the DCC will be assigned to each site. At each PERL monitoring visit the monitor will perform source document verification (on data not previously verified), review essential documents, and meet with the PI. Each visit will follow a predetermined format and the monitors will complete a Monitor Visit Report to record findings.

On-site monitor visits will involve the verification of all source documents and reporting of adverse events. Monitors will also verify that an informed consent form is on file for each subject screened, with appropriately dated signatures and all pages present, that all of the inclusion and exclusion criteria were met for each subject enrolled into the study, and that all the withdrawals and dropouts of enrolled subjects from the trial are reported and explained in the appropriate CRFs. Accrual and retention rates will also be monitored and if these fall appreciably below the projected levels, attempts will be made to identify the reasons. At the end of each monitoring visit, recommendations will be made to correct problems and/or improve the trial quality.

5.2.2 Remote Monitoring and Source Document verification

Remote monitoring will allow for more frequent review of critical outcome measures. It also enables the DCC to identify the need for on-site monitoring of higher risk clinical sites (e.g., sites with data anomalies or a higher frequency of errors, protocol violations, or withdrawals relative to other sites).

5.3. Source Documents

Source documents are essential documents that individually and collectively permit evaluation of the conduct of a clinical study and the quality of the data transcribed. Source documentation is required for all data collected on worksheets and entered into OpenClinica. Some examples of source documents are: hospital records, office charts, lab

reports, x-rays or other diagnostic reports, and select study worksheets. A document is considered as source only if it is the first place the particular data is recorded. Information that was originally collected elsewhere and is transcribed onto a worksheet is not considered source documentation, and thus worksheets are not considered source documents. Source documents must be present to verify all historical data used in determining a subject's eligibility for the study.

5.3.1 Remote Source Document Verification (rSDV)

The following eCRFs require source document upload for remote source doc verification:

- Form 7 Physical Exam-medical record or PE worksheet
- Form 8 Local Laboratory- lab reports
- Form 9 ECG- ECG report
- Form 19 iGFR- Mandatory iGFR Worksheet must be downloaded from the Coordinator Materials link on the PERL website
- Form 45 SAE-admission and/or discharge summary or similar item

Source documents must be de-identified by removing **all** PHI on **every** page. PHI includes names, physical and email addresses, phone/fax number, date of birth, billing account numbers, or any other information that links the document to the patient.

When preparing to upload source documents into OC, please do the following:

- Add Subject ID to the document.
- Collate all source documents related to the specific CRF into 1 file. OC will accept several different formats. PDF is suggested.
- File name should contain subject ID, visit (if applicable) and Form #.
- Upload the source document file into the specified field on each CRF, or in the specified visit in the source document upload section in OC.

Source documents should be uploaded at the time the CRF is completed.

All source data will be removed from OC at the end of the study.

5.3.2 Instructions for Uploading source documents

1. Open CRF
2. Click on "Click to upload file"
3. Click Browse button in the new screen
4. Locate source document file
5. Click Open. File name/address should show in browse box.
6. Click "Upload File". Remember to save form afterwards.

Example:

PERL_007_Physical Examination V1.0

▼ CRF Header Info

Click the flag icon next to an input to enter/view discrepancy notes. Please note that you can only save the notes if CRF data entry has already started.

Exit

The screenshot shows a web-based CRF form titled "Body System". At the top, there are navigation tabs for "Body Sy...(0/65)" and "Other B...(0/2)", along with a "-- Select to Jump --" dropdown menu. Below the tabs, the form content includes a question "A0. Was a physical exam performed at this visit?" with a "Yes" dropdown menu. Underneath is a section labeled "Upload source documents:" which contains a text input field and a "Click to upload file" button. A red oval is drawn around the text input field and the upload button.

5.4 Data Management Procedures and Data Quality Control

Data will be entered and maintained using OpenClinica which is CFR Title 21 Part 11 compliant. The database is created and maintained by the DCC. All data entries and changes to data are audited.

Database quality control performed at the Data Coordinating Center will include range checks, inter-item checks, and missing, incorrect, or questionable values. OpenClinica will generate queries at the time of data entry. The data entry person can resolve them at the time or save them to resolve in a batch. The DCC Data Manager will monitor the discrepancy reports to ensure they are being addressed in a timely manner. The DCC will periodically review data summaries for additional discrepancies. The goals will be to make quality control a continuous process, to make the turnaround time between error detection and correction as short as possible, and to document any changes to the database.

At the end of the study when all data has been entered, data discrepancies are resolved and all quality assurance measures have been completed, the database will be locked. The final database will be stored on the University of Michigan server to assure data security and privacy. At all stages of collection, data will be backed up on regular basis. Access to the database will be password protected to ensure data entry and modification will be limited to authorized personnel.

Chapter 7

Study Medication

7.1. Medication Order Process

Upon randomization and after each post-randomization visit, the Clinical Site should send an e-mail to the Study Pharmacy and attach the PERL Study Medication Order (see Appendix A), along with the Pharmacy Medication Shipping Notice. The order needs to include the participant's initials, Study ID number, name, address and phone number, Visit Number, the most recent local eGFR, the number of days that should be covered by the drug supply, and the allopurinol dose adjustment algorithm of the study. **The PERL Study Medication Order form must be signed by a Study Physician.** Study Coordinator must include their name and FAX number on the Shipping Notice Form.

The study site will decide the number of tablets ordered. As a general guide, if the site has scheduled the participant's next follow up visit, the site should count the number of days until the next visit, and add 7 days worth of study medication (allowing a few extra tablets in case of a re-scheduled visit, or dropped tablets for example). If the site has NOT scheduled the participant's next visit, it should use the last day of the window visit, and add 7 days worth of study medication to determine the amount of tablets to order. The "*number of days the drug to be dispensed in the medication supply*" will be entered on the Medication Order.

All participants are started at the same dose (100mg) at Visit 5, so the site may send the Medication Order immediately following randomization. For visits, 6-15 the site will need to wait until **LOCAL** creatinine results are received so the eGFR can be determined before the order can be sent.

Note: Participants names and addresses will only be shared with the Central Pharmacy for the purpose of mailing the study medication. The Central PERL pharmacy will mail the new bottles of study medication directly to the study participant.* Each mailing will include four bottles of tablets (A, B, C, and D). Participants will be instructed to immediately inform the clinical site upon receipt of the new tablets and mail the previous medication bottles with remaining tablets to the clinical site for drug accounting and compliance assessment. Participants should also be instructed to write on the bottles the date on which they started and the date on which they stopped using that batch of medication.

Participants must be reminded about mailing the previous medication bottles with remaining tablets to the clinical site upon receiving the new medication, and should be queried after the expected receipt of the new medication, to be sure that this has happened.

*At some sites, study medications may be dispensed directly to the study participant at a scheduled In-person visit or by mail from the site following the scheduled In-person visit or Phone study visit.

When ready to ship, the Pharmacist will complete the *Pharmacy Medication Shipping Notice*, indicating date study drug shipped, Subject ID, Randomization Number, a label including name, address, and phone number of participant, number of tablets in each bottle, study drug dosage and FedEx tracking label. Pharmacist will sign/date and fax the shipping notice to the Coordinator listed on the form.

Participants should be reminded at each visit to immediately notify the study personnel if they start any new drug, so that possible interactions with allopurinol can be identified at once and appropriate precautions can be taken which may even include discontinuation of the study drug. They should also call study personnel if they develop any symptoms that may be relevant to the study drug (i.e rash, GI upset).

Lost/Spoiled tablets/Visits outside study windows:

In case of instances where there is a need for replacement study medication, a Refill Prescription may be requested. Examples might include lost study medication bottles, medication becomes spoiled after being dropped or gotten wet, or the next scheduled visit falls outside the window or the amount of medication ordered was insufficient to carry the patient to the next visit. Documentation of lost/spoiled tablets should be noted on the Medication Compliance Worksheet #17, and in the participant’s binder. **ALL left over medication, including pills that are spoiled, must be returned to the study sites and to the Central Pharmacy. (See Sections 7.4 and 7.5)**

7.2. Dosage

At the Central Pharmacy, a pharmacist will determine the allopurinol dose (ranging from 0-400mg) that should be given, based on the participant’s treatment assignment and renal function.

The dose adjustment algorithm is illustrated in **Table 1**.

Subjects randomized to allopurinol will initially take 100 mg per day for four weeks. After that, they will be switched to 400 mg per day if their eGFR is ≥ 50 ml/min/1.73 m², 300 mg per day if their eGFR is in the 25 to 49, and 200 mg per day if the eGFR is in the 15 to 24 ml/min/1.73 m² (Table 1). Allopurinol will be continued at this dosage throughout the study unless the eGFR changes, in which case the dosage will be modified to that appropriate for the new eGFR designation.

Table 1. Allopurinol daily dose.

eGFR (ml/min/1.73 m ²)	Visit 5	Visits 6-15
≥ 50	100 mg	400 mg
25 to <50	100 mg	300 mg
15 to <25	N.A.	200 mg
<15	N.A.	Permanently discontinued

7.3. Medication Administration

All participants, whether they are randomized to allopurinol or placebo, will be given four tablets per day to be taken orally following their first meal of the day. It is advisable to take the pills with food to avoid stomach upset, and to take the pills approximately 24 hours apart. Tablets will be provided in four vials (A, B, C, and D). Alternately, the site may request that the pharmacy ship the medication in pre-packaged blister packs, which will contain ONE DAY'S worth of study medication in each blister.

Participants randomized to allopurinol will receive a dosage of 100 mg as a 100 mg tablet (from vial A) plus three placebo tablets (from vials B, C, D), 200 mg as two 100 mg (from vials A and C) and two placebo tablets (from vials B and D), 300 mg as three 100 mg (from vials A, B, C) and one placebo tablet (from vial D), 400 mg as four 100 mg tablets (from vials A, B, C, D). Subjects randomized to placebo will be given four placebo tablets (from vials A, B, C, D). Blister packs will be packaged to include the same configuration of pills in each blister as is received in the individual bottles.

It is critical that the instructions regarding the vials to be used are reviewed with the patient with each new prescription and that the patient understands is documented in their individual study binder. The importance of taking one tablet from EACH bottle should be stressed, and that they should NOT take all tablets from the same bottle.

Side Effects:

Details of the side effects from allopurinol and RASB can be found in the PERL Protocol Section 3.4.2. Some of the common side effects are listed below:

Common Side Effects of Allopurinol:

- Skin rashes
- Increased frequency of gout attacks
- Reversible liver damage, as well as asymptomatic rises in liver enzymes
- Bone marrow depression
- Unsafe for the fetus or mother during pregnancy and nursing mother

Common Side Effects of RASB:

- Allergic reaction
- Hyperkalemia
- Hypotension
- Increased serum creatinine
- Persistent cough (ramipril)
- Liver damage
- Bone marrow depression
- Fetal and neonatal morbidity and death

Treatment with Antihistamines:

Antihistamines for symptom relief will be given if an allergy to allopurinol or RAS Blockers develops. If a participant develops an allergic reaction, they will be instructed to stop the medication immediately and contact study staff. If a study drug is suspected to be causing an allergic reaction, the Drug Monitoring Committee should be informed and a conference call

should be arranged by the DCC. Complete WS #20 (Adverse Event) and form 20, and WS #45 and form 45 if event qualifies as a SAE.

Note: Prophylactic antihistamines will not be given

Antihistamines **must** be on hand during iGFR visits in case of allergic reaction to iohexol. Please refer to Section 4.5.8 of the MOO, *"Emergency Treatment for Anaphylactic Reaction"*, for detailed information.

7.4. Medication Compliance

Skills will be taught and reinforced at each visit with regard to scheduling and administration of study medication at home and while traveling. Record keeping methods will be taught to help participants monitor tablet usage and enhance compliance. To complement the regular compliance interventions at the scheduled visits, study information and motivational materials (birthday cards, postcards, newsletters, etc.) may be mailed intermittently. **Note:** Each clinic will be responsible to have these items approved by their respective IRB's.

In addition, **at midpoint between clinic visits, participants will be phoned by the clinic staff to review medication administration and the patients understanding of the vials to be used.**

Adherence will be monitored by instructing participants to expect extra pills and to mail the pill bottles with the tablets remaining from the previous prescription to the study center ***immediately*** upon receipt of a new batch of pills. They should be reminded to write the "start" and "stop" dates on the bottles/blister packs before mailing. Each participant should be given a pre-addressed, stamped envelope (bubble bag) to do this. Postage can be pre-calculated by using some pill bottles you have and weighing them with approximately 20 pills inside, and then adding a small amount of money to that number to ensure enough postage. Additional postage may be necessary if more pills are being returned, but otherwise a fairly standard amount of postage should suffice. The number of extra pills included in each supply of medications will be decided by the Study Site as indicated in Section 7.1 above. If necessary, the participant should be called weekly until the left over pills have been received by the clinic. If there are ANY questions about the number of pills returned, assessment of compliance and/or exposure will be much more difficult the longer the span between the participant getting the new ones and mailing the left overs.

Compliance will be calculated on Worksheet #22 and entered into the eCRF #22. If poor adherence is detected (<85%), measures will be taken to increase compliance, such as explaining the purpose of the study again, providing pill minders, and more frequently contacting the study subject by phone. Participants at each visit will be asked about their perceived compliance and about any difficulties with taking the study medications, but the individualized strategies to improve compliance will not be openly linked to the pill counts, i.e. participants will not be informed of the results of pill counting

Participants showing poor compliance will not be withdrawn from the study so every attempt needs to be made to improve compliance. A low compliance/exposure rate would be very detrimental to the study outcome.

7.5. Study Medication Accountability

Quarterly the sites must ship the used study medication bottles back to the Central Pharmacy. The Central Pharmacy will record medication accountability as per their SOPs. **A quarterly reminder should be placed on the site coordinator's calendar.**

A template log for documenting returned Allopurinol/placebo pills is provided at the end of this chapter for your use. This should be maintained in each subject binder to document all study medication received from subjects and returned to the pharmacy for destruction.

Form 022, Compliance and Exposure, must be completed each time medication is received from a subject.

7.6. Blinding Procedures

Study participants, the investigators and research staff at the Clinical Sites, and the PERL Co-Chairs (Drs. Mauer and Doria) will be blinded to treatment assignment whereas designated Data Coordinating Center personnel and the research pharmacy personnel will have access to this information. Serum uric acid values, from which the treatment assignment might be inferred, will not be transmitted to the Clinical Sites. The blind of the study assures that valid, unbiased data is generated during the study.

7.6.1 Breaking the blind

The decision to break the blind must be based on the medical significance and severity of the adverse event. While the safety of the participant is of the utmost importance, the investigator should recognize the fact that unblinding even a single participant can have an adverse impact on the perceived validity of the study results. ***Except in an extreme emergency, the Site Director should be consulted before breaking the blind on any participant.*** If unblinding occurs, the circumstances that led to it will be reviewed and reported to the Steering Committee and the Drug Monitoring Committee. A protocol deviation will be recorded on eCRF #40. Unblinding can only be performed by the Site Director. **The electronic unblinding procedure is detailed in section 9.1 of the MOO.**

Off Hours Unblinding:

The PERL Central Pharmacy is not available during off hours. In case of the need to unblind a participant after "normal business hours," **and the PERL website is down**, sites should contact the ***University of Minnesota Medical Center, Fairview, Inpatient Pharmacy by calling (612) 273-3066, extension 1.*** The following procedure should be followed:

- a) The inpatient pharmacist will be available for emergency unblinding and will have access to blinded treatment assignments 24 hours per day, 7 days per week.
- b) Caller should have subject ID number, and randomization number available for unblinding.

- c) The inpatient pharmacist will then follow the UMMC Fairview standard operating procedures for breaking the blind.
- d) The inpatient pharmacist will notify the UMMC IDS Pharmacy staff of the unblinding.
- e) UMMC IDS Pharmacy staff will notify the PI of the unblinded subject's location.

7.7. Discontinuation of study drug

7.7.1 Reasons for discontinuation

The study drug will be *temporarily* discontinued if a participant:

- Has clinically significant persistent changes from baseline based on laboratory safety assessment results (the response to discontinuation will be monitored to assess whether the drug can be re-instituted, see next paragraph on permanent discontinuations).
- Requires treatment with allopurinol or medications that make allopurinol contraindicated (see 5.5.2 and 9.5).
- Becomes pregnant or breastfeeding (see 5.5.2)

The study drug will be *permanently* discontinued if a participant:

- Experiences an SAE related to the study drug or an intolerable AE such as a persistent allergy or rash.
- Has clinically significant persistent changes from baseline based on laboratory safety assessment results which do not respond to temporary 2-week discontinuation of study drug and re-institution of drug at ½ of the initial dose.
- Develops end-stage renal disease (eGFR ≤ 15 ml/min/1.73 m², institution of chronic dialysis treatment or kidney transplantation) or iGFR decreases by 50% from one measurement to the next or serum creatinine levels double over any 12-month interval in the post-randomization period. Complete WS #20 (Adverse Event) and OC form 20. Complete WS #45 and OC form 45 if an event qualifies as a SAE. Allopurinol, RAS blocker and BP Medication Log should be updated for participant's chart and on eCRF #12. The change in medications will also be captured on the Study Drug Compliance WS #22.

7.7.2 Handling of study drug discontinuation

- Date and reason for drug discontinuation will be recorded as in the above paragraph. All study discontinuations (with the exception of temporary discontinuation due to ampicillin/amoxicillin usage) decided by a clinical site will have to be reviewed and approved by the Drug Monitoring Committee within 10 days from discontinuation of the drug.
- If the study drug is discontinued due to treatment with medications that make allopurinol contraindicated (e.g. amoxicillin/ampicillin), the study drug may be resumed after the contraindicated medication has been discontinued for 4 half-lives. **NOTE: Amoxicillin should be virtually eliminated 24 hours after discontinuation.** If there is uncertainty about the half-life of the contraindicated medication, the study pharmacist should be consulted. If the study drug is discontinued due to pregnancy/breastfeeding, the study drug may be resumed once pregnancy/breastfeeding has ended.
- If the study drug is temporarily discontinued and then re-instated, the end-date of the intervention will remain the same as if the study drug had not been discontinued. All

visits will be carried out as scheduled while the study drug is temporarily discontinued. The dates of stopping and restarting study drug are recorded on the Study Drug Compliance Worksheet # 22 and the Allopurinol, RAS blocker and BP Medication Log.

Unless a participant withdraws consent, all participants that are permanently discontinued from study drug, or who discontinue study medication on their own, will be followed for the full study period (i.e., 164 weeks, including the washout period) and all data will be collected as scheduled. Major attempts will be made to schedule an end-of-study assessment for all participants who are lost to follow-up during the course of the study.

Participants who have withdrawn consent or are lost to follow-up will stay in the study, but will be placed in an Intention to Treat (ITT) category. In an ITT population, none of the participants are excluded and the participants are analyzed according to the randomization scheme. In other words, for the purposes of ITT analysis, everyone who is randomized and starts study drug will be part of the study analysis regardless of how long they participate.

Appendix A

PERL Study Medication Order

Please dispense & ship the Allopurinol/ placebo study drug to:

NAME _____

STREET ADDRESS _____

CITY _____

—

STATE and ZIP

CODE _____

PHONE
NUMBER _____

Number of days to be covered by the medication supply: _____

Visit 5: 100 mg per day or placebo

Visit * ___ (6-15) Date __ / __ /20 ___

*Use the **LOCAL CREATININE** collected on this visit date in eGFR calculation: _____
(ml/min/1.73m²)

Allopurinol/placebo dosing

eGFR (ml/min/1.73 m ²)	Visit 5	Visits 6-15
≥50	100 mg/pbo	400 mg/pbo
25 to <50	100 mg/pbo	300 mg/pbo
15 to <25	100 mg/pbo	200 mg/pbo
<15	N.A.	Permanently discontinued

Physician Name (print): _____ Signature: _____
Date ___ / ___ /20 ___

Coordinator Name (print): _____ Phone: _____
Signature: _____ Date ___ / ___ /20 ___

<i>FAX Completed Prescription to “PERL STUDY PHARMACIST at the appropriate Pharmacy</i>		
United States	Canada	Denmark
(303) 763-9712 or (866) 415-2923	Toronto: (416) 586-8353	+45 43 20 25 86
Virginia Mason (206) 341-0064	Edmonton: (780) 407-5648	

PERL PHARMACY MEDICATION SHIPPING NOTICE

SUBJECT ID _____ P _____ ORDER SHIPPED ____ / ____ / ____
 _____ mo date year

RANDOMIZATION NUMBER: _____ Pilot ID: **J** - _____ N/A

PERL Study Drug Shipped to:

Place Pharmacy Address Label Here

<i>Patient Phone:</i>

*Note: *Refills # is the Visit #*

Number of tablets in each bottle: (A, B, C, D)

Allopurinol/placebo dosing chart:

	Prescribed dose of Allopurinol / placebo
100mg / placebo	<input type="checkbox"/>
200 mg / placebo	<input type="checkbox"/>
300 mg / placebo	<input type="checkbox"/>
400 mg / placebo	<input type="checkbox"/>

Label *Here*

<i>Pharmacist Signature:</i>

Pharmacist, please fax completed form to:

Study Coordinator **FAX:** _____

Site Name: _____ **Phone:** _____

Returned Allopurinol/Placebo Accountability Form

Date	Bottle A returned, Number of Pills	Bottle B returned, Number of Pills	Bottle C returned, Number of Pills	Bottle D returned, Number of Pills	Initials and Signature of Person Accountable for Pill Count

Chapter 6

ECRF Completion Guidelines

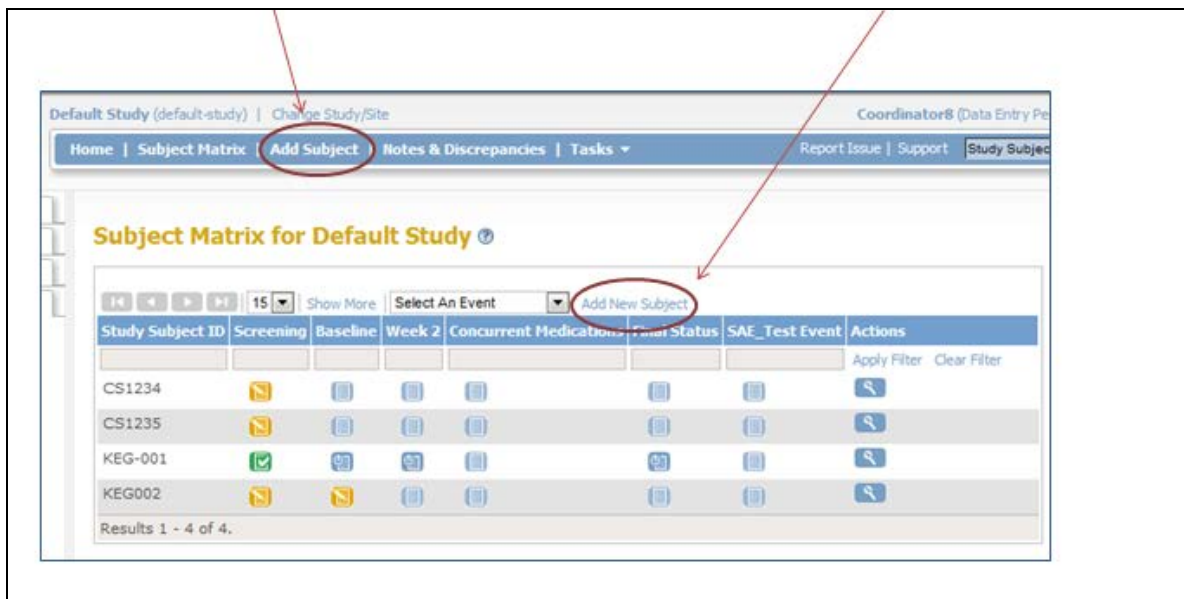
6.1. Enrolling a New Study Participant in OpenClinica:

6.1.1. Participant ID

The PERL participant ID will be the next sequential number on the Participant ID list assigned to each site.

6.1.2. Adding a New Participant in OC

To enroll a participant, you will need to Add the participant to the database. This can be done a couple ways. Select either the Add Subject tab from the top menu bar or from the Subject Matrix screen you can select Add New Subject.



Enter the remaining required information to enroll the participant. All required data will be noted with an "*". Please enter ONLY required information. Secondary ID is not required and should not be used

Default Study: Add Subject ?

* indicates required field.

Study Subject ID: *

Secondary ID:

Date of Enrollment for Study' Default Study ' : *

Sex: *

After entering required information, you may: Save and Assign Study Event, Save and Add Next Subject or Save and Finish to enter participant data later.

6.1.3. Scheduling an Event (Visit)

OpenClinica Events are where you will find the eCRFs for data entry.

After a Participant has been enrolled, Events may be scheduled. You may schedule an event by selecting Save and Assign Study Event from the Add subject screen or navigate to the Subject Matrix screen and select the event icon.

Alerts & Messages

The Subject with unique identifier '02V1234' was created successfully.

Instructions

Other Info

Study: PRIME Initial Training Study

Site: Site 102

Study Subject ID: 02V1234

Start Date: 12-Apr-2013

End Date: 11-Apr-2014

PI: Glen Feak

Protocol Verification/IRB

Schedule Study Event for 02V1234 ?

* indicates required field.

Study Subject ID: **02V1234**

Study Event Definition: *

Start Date/Time: : (DD-MMM-YYYY HH:MM) *

End Date/Time: : (DD-MMM-YYYY HH:MM)

Leave this field blank if the end date/time is not applicable.

Schedule Another Event: (optional)
 Schedule Another Event: (optional)
 Schedule Another Event: (optional)
 Schedule Another Event: (optional)

Select the event, from the Study Event Definition selection and enter the Start Date. The **Start Date is the Visit date.**

Please note: Time fields and End Date are not required

6.2. Entering Data into a CRF

All eCRFs available for entry will be available in the Event Screen. To begin entering data, select the Enter Data action icon next to the eCRF.

The screenshot shows the OpenClinica Enterprise interface. The main heading is "Enter or Validate Data for CRFs in Enrollment". Below this is a form for entering data for a specific study event. The form fields are:

Study Subject ID	CS001
Study Event	Enrollment
Location	N/A
Study Subject OID	SS_CS001
Start Date	21-Jan-2014
End Date/Time	
Subject Event Status	scheduled
Last Updated by	0

Below the form is a table of CRFs in this study event:

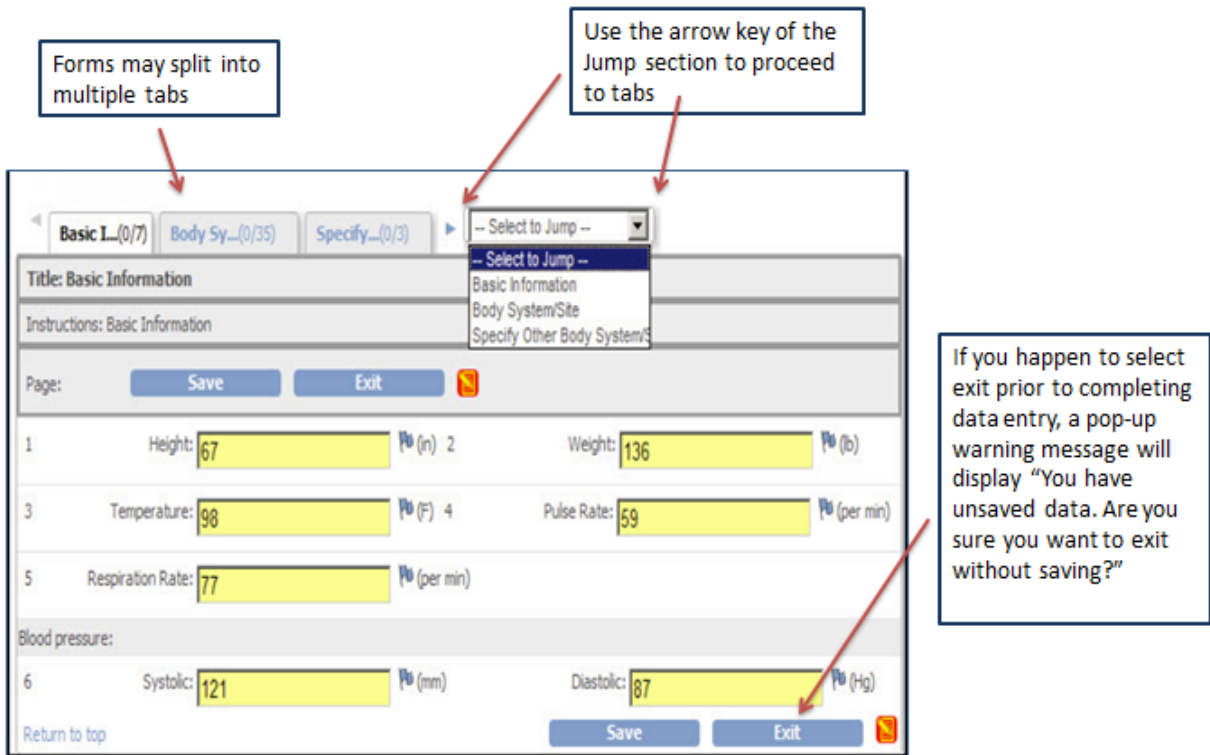
CRF Name	Version	Status	Initial Data Entry	Double Data Entry	Actions
PERL_015_Exemption Request	V1.0	[Icon]			[Enter Data] [View] [Print]
PERL_001_Eligibility Revised II	V1.0	[Icon]			[Enter Data] [View] [Print]

A red arrow points to the "Enter Data" icon in the Actions column for the "PERL_015_Exemption Request" CRF.

From this screen you may also View or Print the eCRF from the Actions menu.

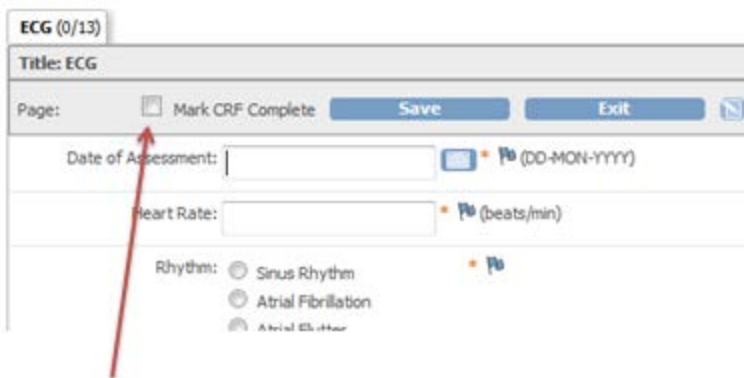
Please note: if you want to View the eCRF only, select the View icon. Do not select the Enter data icon, as OpenClinica will automatically set the eCRF status to Initial Data Entry and it can't be reset.

eCRF Navigation



Mark CRF Complete

Once you have entered all of your data, select the Mark CRF Complete button. If the eCRF has multiple tabs, the Mark CRF Complete button will be located at the top of the entry screen of the last tab.



6.3. Investigator Signature

- In order for the Site Director to sign a form, he/she must sign the entire event. Each form in that event must be marked complete prior to being signed. If any changes are made or discrepancies updated in a form, it will no longer be complete and the signature steps must be performed again after event status is marked complete again.

- The following events/forms require the PI signature. Please refer to section 11 of OC 500 Investigator Training for instructions on how to “sign” events.
 - Eligibility Run-In: Forms 001S-Screening Eligibility, 015-Exemption Request
 - Eligibility Rando: Forms 001R-Randomization Eligibility, 015-Exemption Request
 - SAE: Form 045-SAE
 - Final Status: Form 035-Final Status

6.4. Removing Data

If you mistakenly schedule the wrong event for a subject, enroll a subject incorrectly, or fill out an inappropriate CRF, contact the PERL Data Manager for instruction.

6.5. PERL Schedule of Forms

FORM	Visit 1	Visit 1a	Eligibility Run-in	Visit 2	Visit 3	Visit 4	Visit 4a	Eligibility Rando	Visit 5 Rando Week 0	Visit 6 Week 4	Visit 7 Week 16	Visit 8 Week 32	Visit 9 Week 48	Visit 10 Week 64	Visit 11 Week 80	Visit 12 Week 96	Visit 13 Week 112	Visit 14 Week 128	Visit 15 Week 142	Visit 16 Week 156	Visit 17 Week 164	Unscheduled Visit	Final Status	SAE	AE ConMed, BP med, and Deviation Logs	
			Run-in						RANDO	Allopurinol 200=400 mg or placebo											Wash out/EOS			Signed	repeating Signed	
01S Eligibility			X																							
01R Eligibility Rando								X																		
01RS Rescreen			X																							
02 Demographics	X	X																								
03 Medical History				X		X																				
06 BP and measurements	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
07 Physical Exam	X	X		X			X										X			X	X	X				
08 Local Laboratory Results	X	X			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
09 ECG Report				X		X									X					X	X	X				
10 Central Lab	X	X				X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
10A Central Lab					X	X				X	X	X	X	X	X	X	X	X	X	X	X	X				
11 Skin Assessment						X			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
12 RAS & BP Log																										X
13 Concomitant Medications	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X				X
14 Family History						X			X																	
15 Exemption Request			X					X																		
16 ACR/AER Screening	X	X																								
22 Study Drug Compliance Log										X	X	X	X	X	X	X	X	X	X	X	X	X				
19 IGFR Procedure						X	X								X					X	X	X				
20 Adverse Event Log																										X
25 Unscheduled Visit																						X				
35 Final Status																							X			
40 Protocol Deviation Log																										X
45 Serious Adverse Event																									X	

6.6. CRF Completion Instructions

Refer to the PERL OC training document for additional specifics on how to enter data into OC, and finding and resolving data discrepancies.

All CRFs should be completed within 72 hours of the study visit.

6.6.1. General Instructions:


Not following the instructions below could result in Error Messages which prevent the form from being saved until they are addressed.

Required items: Items with * to the right of the response box are required items. The form cannot be saved if the field is left blank unless a Proposed Resolution is created by clicking on the flag next to the response box.

Moving to next field: You may select the tab key to move to the next field. Do not use the return button to go to next field, as OC interprets a hard return as selecting the Save button. This will close the form or generate discrepancies.

Mark CRF Complete: Mark your CRF complete once you've completed date entry. This will enable the "View within record" feature in the Notes and Discrepancies tab.

Note: CRFs/Events that require PI signature will need to be marked as complete prior to being signed.

Updating Participant ID: If you need to update a participants ID, go to the Subject Matrix screen, locate your participant and selected the view  icon under the Actions section, this will take you to the Subject record screen. On the top of the screen, select Study Subject Record and then Edit Record.

Data types: There are various data types within the CRFs. We've listed below the data types you will experience for this project:

Single select: Radio buttons are always single select. Drop down selections are single select unless otherwise noted with a 'select all that apply' statement.

Multi-select: Check boxes are always multi-select, but there may be some cases where we are controlling these as single select. Multi-select will be identified with a 'select all that apply' statement.

Dates: Use the pop-up calendar or enter in the DD-MMM-YYYY Format (13-MAY-2013). Partial dates are accepted for some fields but always enter as much of the date that is known. Example: (MAY-2013) or (2013). Fields where partial dates are accepted will be noted in the CRF specific sections, below. If nothing is noted, a full date is required.

Times: Use the 24-hr (military time) format with the colon (Example: 4:00 pm = 16:00).

Number values: Number fields may have various limits set on them. Some may allow decimals some may not. In some cases we may be restricting the number of characters that can be entered as well. Any restrictions/allowances set on fields will be noted in the CRF specific sections, below.

Calculations: If we will be calculating a value for you, the calculation field will appear grayed out.

Text: Some fields are free text fields, and they will accept alpha or numeric entry. These have a 255-character limit.

Log forms: Log forms are a way to capture repeating data or more than one set of data at a single data collection time period. To include an additional row of data, click on the Add button, located under the last row of the log. Please note: once a row has been added and saved, it can't be removed. If a row of data needs to be removed, after save, each data field will need to be reset or deleted by the Coordinator.

Upload Source Documents: You can upload most file types by clicking on the upload file button. A browse screen will pop up to allow for selecting the file to upload. Any source document should be de-identified (all PHI removed) and contain the participant ID number on it. The file should be named "Participant ID_Visit Type_Form #". Example: "02AP0001_Visit5_Form_3.pdf"

6.6.2 Individual Form Completion Instructions

FORM 001S-ELIGIBILITY FOR RUN-IN

This form is completed after the Visit 1, Screening Visit.

There are 3 sections to this form, sections A-C. Ensure each section is completed. Each section should be saved before moving to the next section. If you attempt to move to the next tab without saving data first, you will lose the data. A pop-up message will warn you of this first.

NOTE: This form should be completed in the OC database as soon as possible but no more than 48 hours after the participant signs the informed consent. Not completing this form correctly and in its entirety will prevent randomization from occurring.

Section A. Inclusion Criteria

A0. If the participant is from the pilot study, answer this question Yes. An additional question will pop-up asking for the Pilot participant ID. The remaining questions in A and B can be skipped for pilot participants.

A1-A10. For non-pilot participants, all questions must be answered. All answers in this Section must be "Yes" for the participant to be eligible for the run-in period, with the exception of A3. "Not done" response option is provided (in form Version 1.0 only) if participant is determined to be ineligible prior to determining all criteria.

Section B. Exclusion Criteria

For non-pilot participants, all questions must be answered. All answers in this Section must be "No" for participant to be eligible for the run-in period. "Not done" response option is provided (in form Version 1.0 only) if participant is determined to be ineligible prior to determining all criteria.

C1. Eligibility Status

Eligible for Run-in: All Inclusion responses must be "Yes" (with the exception of A3) and all exclusion responses must be "No."

Eligible (Pilot Participant): For pilot participants only, A0 must be yes.

Ineligible for Run-in: At least one inclusion should be "No" (other than or in addition to A3) or at least one Exclusion should be "Yes".

Eligible for Run-in by Exemption: Although exceptions/exemptions are not expected, the option is included in the event there is such a case. If the participant violates an inclusion/exclusion criterion and an exemption is approved, check eligible by exemption. Refer to instructions for Form 15 Exemption Request for additional instructions on how to request an exemption.

FORM 001RS-ELIGIBILITY RE-SCREEN

This form is completed after the Visit 1, Screening Visit, if a re-screening visit is being considered

A1 This is the date on which you decide that a re-screen visit (Visit 1A) will be considered

A2 Please indicate which criteria were not met at Visit 1. These criteria will be re-assessed at Visit 1A

A3 Please enter the estimated date in which the subject will return for their Visit 1A

NOTE: Visit 1A must occur at least 4 weeks after Visit 1

FORM 001R –ELIGIBILITY RANDOMIZATION

This form is completed after visit 4, prior to Randomization.

Section A. Inclusion Criteria

A1. This question must be answered. Verify that participant continues to meet all inclusion criteria (applicable to form Version 1.0 only).

A2. This question must be answered. Verify that the participant has a valid baseline (Visit 4) iGFR measurement.

Section B. Exclusion Criteria

B6. This question must be answered. Complete this once the results of the HLA B*58:01 genotype is known. If the participant is positive for this gene, mark this "Yes". If this is answered "Yes", the subject is not eligible for randomization.

B10. This question must be answered. Complete this at the end of Visit 4 (or 4a if required). If this is answered "Yes", the subject is not eligible for randomization.

NOTE: If this form is not completed correctly, in its entirety, randomization will not be allowed and an error message will appear when attempting to randomize the subject. Should you receive this error message, please review this form in OC.

Section C. Eligibility Status

Eligible for Randomization: A1 must be "Yes" and all exclusion responses must be "No."

Ineligible for Randomization: A1 should be "No" or at least one Exclusion should be "Yes".

Eligible for Randomization by Exemption: Although exceptions/exemptions are not expected, the option is included in the event there is such a case. If the participant violates an inclusion/exclusion criterion and an exemption is approved, check eligible by exemption. Refer to instructions for Form 15 Exemption Request for additional instructions on how to request an exemption.

FORM 002-DEMOGRAPHICS

This form is completed at Visit 1.

A1: Date of consent should be entered in dd/Mmm/yyyy format.

A2: Date of birth should be entered in dd/Mmm/yyyy format.

A3: Once Date of birth is entered, click on the Age field, and the database will calculate the participant's age.

A4a: If "Female not of child-bearing potential" is chosen in 4, a drop down menu will appear to indicate the reason. Select all that apply. If "Other" is chosen, indicate the reason in the text box provided.

A5-A8: Enter data as directed.

A8: If A8 is answered "Yes", a drop down menu will appear.

A8c: Total years smoked allows for a decimal to the tenths place.

A9: If answered "Yes," a text field will appear that asks for average number of drinks per week.

FORM 003-MEDICAL HISTORY

This form can be completed at Visit 1, 2 or 4 and should be completed only once. Completing this form in more than one visit will result in a discrepancy.

There are 8 sections to this form, sections A-H. Ensure each section is completed.

A-H: If a specific condition is checked, a check box will appear to indicate if the condition is ongoing (current). A selection of "Yes" (ongoing) or "No" (not ongoing) is required.

A-H: If medical condition is not specified, choose "Other" from drop down list. A comment box will appear to enter the medical condition and whether the condition is ongoing. If "Other" (A19) is selected, an entry must be made in the "If Other, Specify" text field. A selection of "Yes" (ongoing) or "No" (not ongoing) is also required.

H1: If Allergies is answered "Yes," a comment box will appear to list allergens.

H2: If pregnancy question is answered "Yes," the number of pregnancies and number of live births should be recorded.

H3: If answered "Yes", completion of the Hospitalizations Log tab is required.

FORM 006-BLOOD PRESSURE MEASUREMENTS

This form is completed at all study visits. Data is required at visits 4, 4a (if needed), 11, 15 and 16, as well as any unscheduled visits where an iGFR procedure was repeated / reattempted.

There are 2 sections to this form. Ensure section 1 is completed and saved in order for the averages to be calculated in section 2. Ensure section 2 is saved as well.

A1: Weight is entered in kg.

A2: Height is entered in cm.

Upload Source Documents: De-identify any original medical records or source worksheets, add participant ID and upload the file.

B1-B3: Enter data as directed. Mark "Not done" if HR or BP were not taken.

FORM 007-PHYSICAL EXAM

This form is completed at Visits 2, 4 (4a if determined necessary), 11, 16, and if necessary any unscheduled visits.

Upload Source Documents: De-identify any original medical records with physical exam results or PE worksheets, add participant ID and upload the file.

A1-A10: Answer each item. If an item was not done, select "Not done" for that item.

A1-A10: If answered "Abnormal," findings must be described. Choose all that apply.

A1-A10: If "Other" is chosen for type of finding, a comment box appears to enter information on findings.

FORM 008- LOCAL LABORATORY RESULTS

This form is completed at all study visits except for Visit 2.

There are 5 sections to this form, sections A-E. Ensure each section is completed.

Upload Source Documents: Since this form collects safety data, source documentation will be reviewed regularly. De-identify any original lab reports, add Subject ID, and upload the file.

- Each item must either have a value entered or the "Not Done" check box checked.
- Enter a date for all labs that are completed.
- Comments such as QNS or ND will not be accepted. QNS should be recorded as "Not Done."
- Some labs will provide results in different units other than what is on this form. Convert the results to the units provided on the form.

- Use the earliest value if a lab is done more than once on the same day unless it was repeated due to a testing error.

eGFR is entered in Section E for Visits 1 (using Central Lab creatinine), and 6 through 15 (using local lab creatinine) only. DO NOT enter creatinine or eGFR values in Section E for Visits 3, 4, 16 and 17; leave the visit dropdown on the default (Select) and check the “Not Done” checkbox.

FORM 009-ECG REPORT

This form is completed at Visits 2, 4, 11, 16, and any unscheduled visits (if required).

Upload Source Documents: Since this form collects data on safety, source documentation will be reviewed regularly. De-identify any original medical records, add Subject ID and upload the actual ECG tracing, signed by the PI or Co-I.

A1-A2: Enter data as directed.

A3: If answer “Abnormal,” a menu of findings appears. Check all that apply.

A3a: If “Other” is chosen, a comment box appears to enter information on abnormality.

A3b: If abnormal finding is clinically significant, report this on the AE log.

FORM 010-CENTRAL LAB SPECIMEN COLLECTION

This form is completed at Visits 1, 3, 4, 4a (if required), and Visits 6-17.

There are 3 sections to this form, sections A-C. Ensure each section is completed and saved.

Sections A-C: If “Yes” is chosen for any answer, date of collection or shipment must be entered.

B1. If ACR/AER Collected is “Yes”, enter date collected and which type of urine(s) were collected for the visit.

C3. If urine aliquots were sent for the biorepository mark “Yes” and indicate if the protease inhibitor was added to the specimen.

FORM 010A-CENTRAL LAB SPECIMEN COLLECTION

This form is **ONLY** completed at Visit 3, or if the subject is eligible to skip Visits 2 and 3, at Visit 4. It should **NOT** be completed at any unscheduled visit.

The differences in this form, as compared to Form 010, are: the inclusion of "A3. HLA B*5810 testing", removal of A2, and removal of Section C

FORM 011-SKIN ASSESSMENT

This form is completed at Visits, 6-17, and any unscheduled visits (when required), whether the visit is in-person or conducted over the telephone

A1-A3: Answer each item. If an item was not done, select "not done" for that item.

A1: If answered "Yes," check boxes for symptoms appear.

If "Fever" is selected, the duration of the temperature, and the maximum temperature in Celsius or Fahrenheit should be entered. If the temperature is unknown, mark "Temperature unknown."

A2: If answered "Yes," check boxes for symptoms appear.

If "Red or purple rash" is selected, a checklist of rash locations appears. Mark all that apply.

If "Hives" is selected, a checklist of areas of hives appears. Mark all that apply.

If "Blisters" is selected, a checklist of areas of blister appears. Mark all that apply.

If "Shedding" is selected, a checklist of areas of shedding appears. Mark all that apply.


If "Denuded skin" is selected, a checklist of areas of denuded skin appears. Mark all that apply.

A3: If "Yes" is selected for any condition, a checklist of symptoms appears. Mark all that apply.

FORM 012-RASB MEDICATION LOG

This form is initially completed at enrollment into the study then reviewed and updated (as necessary) at every visit.

Upon opening the form for data entry, questions relating to the subject's RASB medication status at the time of enrollment in the study are presented. This portion of the form is completed only once. Once done, only the log portion of the form (second tab) is to be reviewed at every visit and updated (as needed).


PERL_012_RAS and BP Medication Log t0.9  **TESTforTRAINING**

▼ CRF Header Info


◀ **RAS at ...**(0/12) **RAS &am...**(0/12) ▶ -- Select to Jump -- ▼


Title: RASB Medication Status at Enrollment

Instructions: **The following questions relate to the subject's RASB medication status at the time of enrollment in the study.**

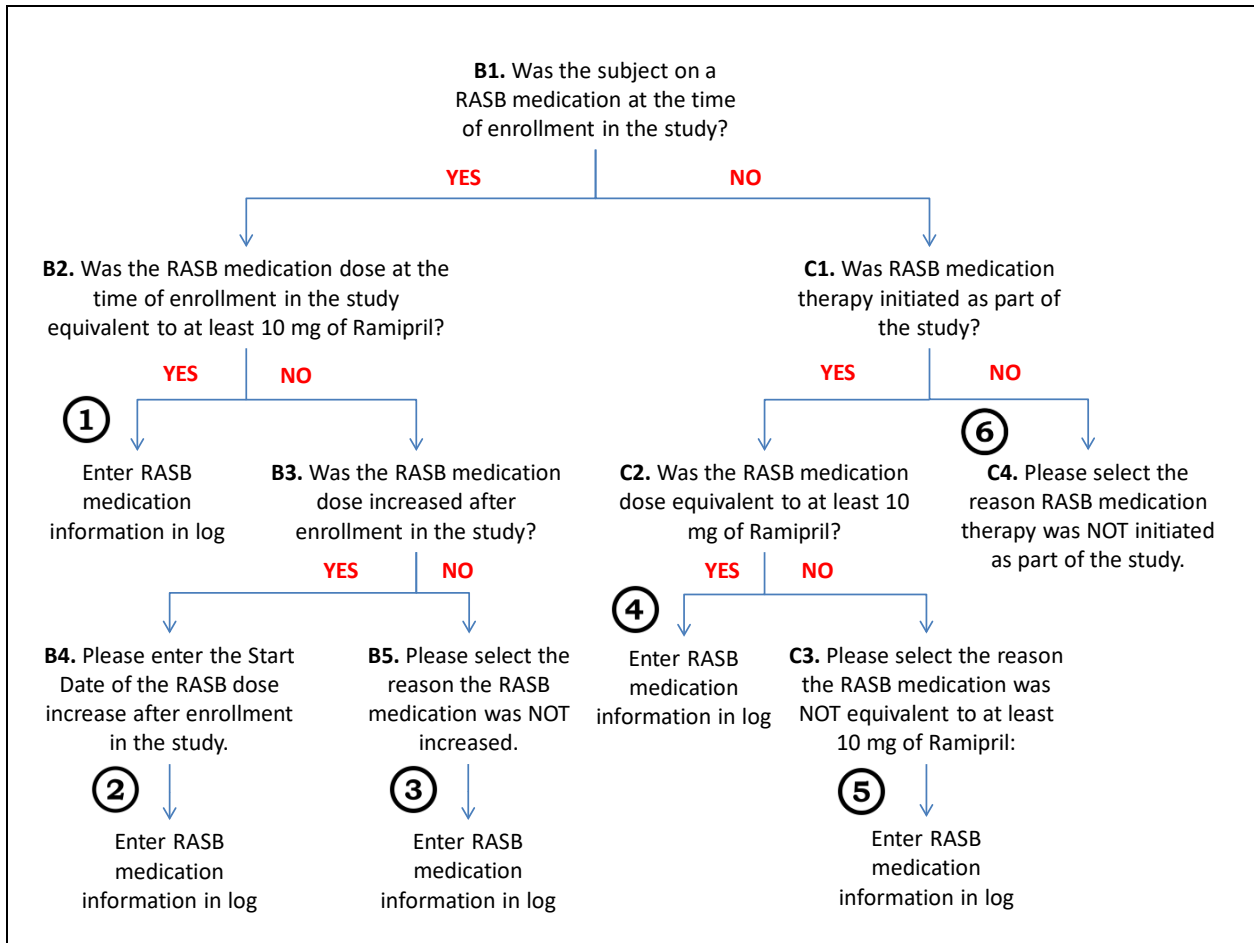
Page: 

B1. Was the subject on a RASB medication at the time of enrollment in the study?

(Select) ▼ * 

[Return to top](#) 

On the next page is a chart illustrating the flow of data entry. There are six paths that can be followed, based on each Yes/No question. Five of those paths result in entering data on the RASB medication log (the second tab). The sixth path results in no additional data entry. Please note both B5 and C4 have “Participant opposed” and “Healthcare provider opposed” as possible selections. Selecting either one of these reasons in answer to B5 or C4 constitutes a protocol deviation; therefore, please confirm that a protocol deviation has been submitted.



Once complete, click “Save” on the first tab and you’ll be taken to the second tab – the RASB medication log.

PERL_012_RAS and BP Medication Log t0.9 TESTforTRAINING

CRF Header Info

RAS at _[0/12] RAS Ram_[0/12] -- Select to Jump --

Title: RASB Medication Log
 Instructions: Enter ONLY RASB medications on this log. All other medications, including BP meds, are entered on Form 013 - Concomitant Medications Log.

Page: Mark CRF Complete

RASB Medication Name:	If Other RASB Specify Generic Name:	Total Daily Dose:	Dose Units:	If Other Units, Specify:	Subject started medication PRIOR to enrollment in the study:		Start Date:	Ongoing:	Stop Date:	Reason Stopped:	If Other Reason Stopped, Specify:
					Yes	No					
(Select) ▾	<input type="checkbox"/>		(Select) ▾		<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>		(Select) ▾	<input type="checkbox"/>

Return to top Mark CRF Complete

If there is no RASB information to enter on the log, exit the form and you are done with data entry.

Note that holding your cursor over a column heading will bring up a hover note giving additional information about the data to be entered. Complete each column as follows:

RASB Medication Name: Only RASB medications are listed, and they are listed by generic name only. If subject is on a combination medication, only the RASB portion is recorded here. Please refer to the following list for brand names known at the time of this writing and their corresponding generic name.

RASB_Brand_Name	RASB_Generic_Name
Accupril	Quinapril
Altace	Ramipril
Atacand	Candesartan
Avapro	Irbesartan
Benicar, Olmetec	Olmесartan
Capoten	Captopril
Coversyl	Perindopril
Cozaar, Hyzaar	Losartan
Diovan	Valsartan
Edarbi	Azilsartan
Lotensin	Benazepril
Mavik	Trandolapril
Micardis	Telmisartan
Monopril	Fosinopril
Prinivil, Zestril	Lisinopril
Tekturna	Aliskiren
Teveten	Eprosartan
Univasc	Moexipril
Vasotec	Enalapril

If Other RASB Specify Generic Name: It is highly unlikely you will come across any RASB medications that are not listed above. If you do, please Google the med to ensure it's not a new brand name for one of the generics listed. If it is, in fact, a new medication, select "Other" in the RASB Medication Name field and enter the generic name of the new medication.

Total Daily Dose: Please note that this is the **total daily dose** not the strength of the medication. Therefore, if the subject takes more than one pill a day, the totally daily dose is the number of pills taken in a 24-hour period times the strength of the medication. For example, if the subject takes 2 pills a day and the strength of the pills is 12.5 mg, the entry in the Total Daily Dose fields would be 25 (2 times 12.5 = 25).

Dose Units: Select the dosage units of the RASB medication. It is expected that mg (milligrams) will be the units for all RASB medications; however, mcg (micrograms) and other are provided as well.

If Other Units, Specify: If for some reason the RASB medication is in some unit other than those provided, enter it here and be sure to select “Other” from the Dose Units dropdown box.

Subject started medication PRIOR to enrollment in the study: This question must be answered. If “Yes”, then a Start Date is not required (though you can enter one if you have it). If “No”, then a Start Date must be entered.

Start Date: Required if the subject started the RASB medication AFTER enrollment in the study.

Ongoing: Check this box if the subject is still on the RASB medication.

Stop Date: If the subject stops the RASB medication or the dose is changed, enter the date this occurred.

Stop Date Unknown: Check this checkbox only if the Stop Date is unknown and absolutely unretrievable.

Reason Stopped: If the subject has stopped taking a RASB or the dose has changed, select one of the following options:

- Not tolerated/side effects – subject is unable to tolerate the RASB medication as evidenced by side effects.
- Cost prohibitive – subject is unable to bear the cost of the RASB medication. Please note that this option is not sanctioned by study leadership and should not be accepted unless absolutely necessary.
- Participant’s decision – subject has decided, for whatever reason, that they want to stop the RASB medication. Please note that this option is not sanctioned by study leadership and should not be accepted unless absolutely necessary.
- Healthcare provider’s decision – subject’s healthcare provider has decided, for whatever reason, that the subject should stop taking the RASB medication.
- Changed dosage – the dose of the current RASB medication has been changed.
- Changed RASB – subject is stopping the current RASB medication and starting a different RASB medication.
- Pregnancy or breast-feeding – subject is currently pregnant or breastfeeding.
- Other – none of the other selections apply; be sure to specify the reason stopped in the “If Other Reason Stopped, Specify” field.

If Other Reason Stopped, Specify: If none of the selections in the Reason Stopped dropdown apply, then enter the reason here and be sure to select “Other” from the If Other Reason Stopped, Specify dropdown box.

If there is an additional RASB medication to enter, click the “Add” button to add another line and continue data entry. Otherwise, click the “Save” button. If all data has been entered correctly, the form will close. If discrepancies fire, address them (when the flag is red; and be

sure to change the status to "Propose resolution"). Click the "Save" button again and the form will close.

Discrepancies – some reminders

The process order is important so you can avoid duplicate discrepancies:

1. Enter data
2. Save
3. Discrepancies fire
4. Make corrections to data incorrectly entered (do not enter any notes by clicking on a **gray** flag)
5. Save again (you'll be taken to the next tab or the form will close)
6. Return to tab (or reopen form)
7. Address any red-flagged discrepancies by clicking on the red flag and explaining, making sure you change the status to "Resolution Proposed"

FORM 013-CONCOMITANT MEDICATION LOG

This Form is updated throughout the course of the study. Hold your cursor over a column heading for "hover tips" giving a more detailed description of what is to be entered.

- This log is used to record all prescription (with the exception of RASB meds, which are entered on Form 013) and over-the-counter medications, including vitamin supplements taken during the course of the study.
- Include immunizations on this log as well.
- The study medication is NOT entered on this log.
- Enter combination meds separately; i.e., each medication in the combo med should be listed as an individual medication. If part of the combo is a RASB med, that part is to be listed on Form 012.
- If different doses of a medication are taken in the same day, each dose is to be listed as a separate medication.

Medication Name: Use the drop down list to select the name of the medication. A list of the medication names appearing in the drop down list, as well as brand names, classification and indication, is provided for reference in the Coordinator Dropbox (PERL Worksheets folder) on the PERL website. Please search this list before resorting to selecting "Other."

If Other Medication Name, Specify: In cases where the medication name does not appear in the drop down list and you've selected "Other," enter the generic name of the medication here. It is recommended you do a Google search to ensure you are entering the generic name and spelling it correctly.

Dose: Enter the amount of medication taken at any one point in time as a number. Non-numeric characters are not accepted. If dose is not known, leave this column blank and select

"Unknown" in the next column ("Dose Units"). For insulin **only**, the total dose taken in a day can be entered as one entry.

Dose Units: Select the units of the dose entered in the prior column. If Dose is unknown, select "Unknown" here. If the correct unit does not appear in the drop down list, select "Other."

If Other Dose Units, Specify: If "Other" was selected in the "Dose Units" column, enter the correct unit here.

Dose Frequency: Select the frequency at which each dose is taken. Both "Unknown" and "Other" options are available for use when needed. Note that insulin can be entered as a total daily dose, with the selection of "QD".

If Other Dose Frequency, Specify: If "Other" was selected in the "Dose Frequency" column, enter the correct frequency here.

Indication: Select the reason the medication is being taken from the drop down list. It is particularly important to record here if a medication is being taken to treat hypertension. If the indication does not appear in the list, select "Other." There is also an "Unknown" option, if needed. If the medication was used to treat an adverse event, use the same term that was used on the adverse event log

If Other Indication, Specify: If "Other" was selected in the "Indication" column, enter the correct indication here.

Start Date: If the medication was started prior to the subject being enrolled in the study, this can be left blank. A partial date can also be entered (month and year, or just year). If the medication was started after the subject was enrolled in the study, a complete start date is to be entered.

Subject started medication PRIOR to enrollment in the study: Check "Yes" if the medication was started prior to the subject being enrolled in the study; otherwise, check "No."

Ongoing: Check this box if the subject is still taking the medication.

Stop Date: If the subject stops taking a medication, enter the date they stopped here. A partial date can be entered (month and year, or just year); however, make every effort to get a full date.

Stop Date Unknown: If the stop date is absolutely unknown and irretrievable, check this box.

Reason Stopped: Select the reason the medication was stopped from the drop down list. If the reason does not appear in the list, select "Other." There is also an "Unknown" option, if needed.

If Other Reason, Specify: If "Other" was selected in the "Reason Stopped" column, enter the correct reason here.

FORM 014-FAMILY HISTORY

This form is completed at Visit 4.

There are 4 sections to this form, sections A-D. Ensure each section is completed.

Relative: Use the drop down list to select the type of familial relationship.

Alive/Deceased: Use the drop down list to select an answer. If status is unknown, mark "Unknown."

If Deceased, Cause of Death: Use the drop down list to select the cause of death. If the cause is not on the list, select "Other" and specify the cause in the space provided. If the cause is unknown, mark "Unknown." If the status of the prior question, "Alive/Deceased", is marked as unknown, then this question should be left unanswered with the default value (select) selected in the dropdown. This question should only be answered if the relative in question is known to be deceased.

No History: Mark this box only if the relative doesn't have a history of any of the conditions listed.

Medical Conditions: Use the drop down list to select an answer. If status is unknown, mark "Unknown."

Other: If relative has a history of another medical condition, enter it into the box provided.

FORM 015-EXEMPTION REQUEST

In the rare case where the patient does not meet all inclusion/exclusion criteria but the Site Director believes that the patient should be enrolled in the study, an exemption request may be filed.

A1-A2: Only 1 response can be selected for each. If there are more than one eligibility criteria violations, the patient is not likely to be a candidate. However, additional items can be recorded in A3.

A3: This is required. Enter the reason and save the form. This will generate an email to the exemption committee. An email may then be sent to the PI and primary coordinator requesting additional information. The exemption committee will respond to the request within 48 hours of receipt. An email with the results will be sent to the site coordinator and PI. The site coordinator should then complete A4, A4a (if A4=No) and A5 of the form

FORM 016-ACR/AER SCREEN

This form is completed at Visit 1 for all screened subjects.

Upload Source Documents: Since this form collects data on inclusion criteria, source documentation will be reviewed regularly. De-identify any original lab reports, add participant ID and upload the file to the Visit 1 field on the Source Document Uploads form in the Source Documents event.

Data is entered for the criteria used to document microalbuminuria or moderate macroalbuminuria (or lack of albuminuria) at screening. We expect one criteria to have been considered: Albumin excretion rates (AER), Albumin Creatinine ratios (ACR) or eGFRs, with ACR being the preferred.

A1a: Check this box if AER was the criteria considered at screening. RASB status must also be selected from the dropdown box.

A1b: Check this box if ACR was the criteria considered at screening. RASB status must also be selected from the dropdown box.

A1c: Check this box if eGFR was the criteria considered at screening. The slope calculation must also be entered in the box provided.

Record the values of AER, ACR or eGFR that were considered at screening:

AER: Enter the dates in the first column; enter the values in the third column; select the appropriate units* in the fourth column (the second and fifth columns are left blank).

ACR: Enter the dates in the first column; enter the values in the second column; select the appropriate units* in the fourth column (the third and fifth columns are left blank).

eGFR: Enter the dates in the first column; enter the values in the fifth column (the second, third and fourth columns are left blank).

eGFR slope will be calculated to align with the intent of the protocol. If sites have entered more eGFR values than required to meet the intent of the protocol, they will be asked to recalculate the slope using only the values needed. Additional eGFR values entered but not required for the slope calculation can remain on the form.

*Units: If results are expressed in mg/g, select mg/24 hr as they are equivalent. If results are expressed in µg/min, select mcg/min as they are equivalent.

FORM 019-IGFR PROCEDURES

This form is completed at Visits 4 (4a if blood pressure too high at Visit 4), 11, 16, 17 and unscheduled visits (if procedure needs to be repeated or reattempted). The form is completed even if the procedure was attempted but not performed.

Upload Source Documents: Since this form collects data on one of the primary outcomes, source documentation will be reviewed regularly. De-identify any original lab reports, add subject ID, and upload the file.

A1: If “No” is checked, a drop down menu of reasons is provided. Check all that apply.

A1: If the reason is not listed, choose “Other” and provide the reason in the box provided.

A2: Enter the date that the procedure was performed.

A3: Enter the time that the Omnipaque injection ended; this will be the start time (T0)

A4-A8: The projected time will be calculated based on the time entry in A3; please enter all ACTUAL draw times and glucose values.

FORM 020-ADVERSE EVENTS LOG

At each visit, query the participant and review the medical record for any new medical conditions. Obtain the status of any previously reported conditions. All non-serious adverse events are recorded on this log. For each new AE click on the “ADD” button.

- If a row was added inadvertently, click on the “X” button at the end of the row to remove it. If the form has already been saved, then you cannot delete the new row. If it was not your intention to add a row, and you cannot delete it due to having previously saved, please ensure that all response fields are blank and dropdowns returned to their default value of (select). The row can then be ignored during analyses.

Adverse Event: This is a required field. Choose an event from the drop down list. Enter one event per line. If the event is not in the list, choose Other, and Specify in the next column. This should be only 1-3 words, and indicate the overarching diagnosis of the event; this is not a full summary of the entire event.

Onset Date: This is a required field. Enter the date the Adverse Event began. If actual date is unknown, enter an estimate. Partial dates are not accepted.

End Date: Enter the date the Adverse Event ended. If actual date is unknown, enter an estimate. Partial dates are not accepted (if the AE is ongoing, leave this field blank). When AE has ended, update this field with the AE end date.

Severity: The severity of the Adverse Event should be defined by using the following criteria:

- **Mild** – events are usually transient, requiring no special treatment and do not interfere with the patient’s daily activities. Mild events are easily tolerated.
- **Moderate** – events traditionally introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures. Moderate events may cause some interference with daily activities.
- **Severe** – events interrupt a patient’s normal daily activities and traditionally require intensive therapeutic intervention. Severe events are usually incapacitating.

Expected or Unexpected: Indicate if this is an expected adverse event, as outlined in the protocol and MOO Chapter 8

Relationship to Allopurinol: For allopurinol, indicate if it had a causal effect on that Adverse Event, as reported by the Clinician/Investigator.

Relationship to Ramipril or other ACEI or ARB: Indicate if it had a causal effect on that Adverse Event, as reported by the Clinician/Investigator.

Action Taken regarding Allopurinol: Indicate the action taken with allopurinol in response to the AE (report any action taken for ramipril such as dose change or discontinued, on Concomitant Medications Form).

Outcome: Indicate the outcome of the event. If the event is ongoing, mark "Ongoing." If the outcome is unknown, mark "Unknown."

Treatment Required: Indicate if medication or other treatment was required to treat this event (if yes, enter details on Form 13 Concomitant Medication Log).

PERL_022_STUDY DRUG COMPLIANCE AND EXPOSURE (this form is completed at visits 6 through 17)

Data Entry Instructions Upon opening the form for data entry, all fields are hidden with the exception of the lead-in question:

PERL_022_Study Drug Compl & Expo t1.34 0002TEST

CRF Header Info

Exposure (0/10) Compliance (0/38) Compliance (0/2) -- Select to Jump --

Title: Study Medication Log

Instructions: Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period. The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Page: Save Exit

Has the subject permanently discontinued the study drug prior to this dosing period?:

(Select) *

Return to top Save Exit

Instructions: Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period. The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Page: Save Exit

Has the subject permanently discontinued the study drug prior to this dosing period?:

If subject has been permanently taken off the study drug prior to this Dosing Period, you do not have to fill out any more of this form.

Return to top Save

Holding the cursor over the question statement reveals

a note providing additional clarification.

If the subject has been permanently taken off the study drug **prior to this Dosing Period***, select "Yes" from the dropdown box, save the form, and data entry for this form is complete. Close the form by clicking the "Exit" button.

Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period. The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Save Exit

Has the subject permanently discontinued the study drug prior to this dosing period?:

Yes

Save

Select "No" from the dropdown box if the subject is still on the study medication or was on the study medication for any amount of time during this Dosing Period. Click the "Save" button and the Study Medication Log

appears. This is a log detailing how the study drug was taken for the entire Dosing Period. If there were no Discontinuations (pills subject was **instructed** not to take) during the Dosing Period, there will be only one line on this log. If there was one or more Discontinuations (pills subject was **instructed** not to take) during the Dosing Period, there will be as many lines on this log as it takes to report all periods of time when the subject was taking the study drug, a reduction in the study drug and all periods of time when the subject was **instructed** not to take the study drug.

PERL_022_Study Drug Compl & Expo t1.34 0002TEST

CRF Header Info

Based on your answers, you need to answer additional questions below. =====

[Please complete the Study Medication Log]

Exposure (1/10) | Compla... (0/38) | Compla... (0/2) | -- Select to Jump --

Title: Study Medication Log

Instructions: Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period. The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Page: Save Exit

Has the subject permanently discontinued the study drug prior to this dosing period?: No

Start Date	Start Date Unknown	Stop Date	Stop Date Unknown	Dosage Dispensed by Pharmacy	Type of Change	Other Type of Change	Reason for Change (select all that apply)	Other Reason for Change
	<input type="checkbox"/> Unknown		<input type="checkbox"/> Unknown	(Select) (mg/day)	No change		<input type="checkbox"/> Lab safety assessment results <input type="checkbox"/> Allopurinol contraindicated <input type="checkbox"/> Off-label allopurinol treatment required	

Add

Return to top Save Exit

Start Date: The Start Date for this dosage or the Start Date of a period of time the subject was not taking the study drug. The first Start Date will be the beginning of the current Dosing Period. If additional line(s) are needed, click the "Add" button and succeeding start dates will be the previous line Stop Date plus 1 day.

Start Date Unknown: Check this checkbox if the Start Date is unknown and absolutely unretrievable.

*The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills after the next visit.

Stop Date: The Stop Date will always be the last day taking pills of the same dose (i.e., a change in dose is reported on a new line) or the last day not taking pills before restarting the study drug. The last End Date will be the end of the current Dosing Period.

Stop Date Unknown: Check this checkbox if the Stop Date is unknown and absolutely unretrievable.

Dosage Dispensed by Pharmacy: If subject stops taking the study medication, for whatever reason, this will be "0" (zero). Otherwise, it will be the study medication dose dispensed by the Pharmacy. Options are 0, 100, 200, 300, and 400. This is a required field.

Type of Change: Select the type of change in dose (only one) this line of the log represents. Use the following as a guide (this is a required field):

- **No change** – no change in dose (this typically applies to the first entry of the Dosing Period and refers to the dose not being changed from the previous dosing period)
- **Permanently discontinued** – subject has permanently discontinued the study medication during this Dosing Period
- **Temporarily discontinued** – subject has temporarily discontinued the study medication for a period of time; they are expected to restart at some point in time
- **Change in dose** – a change in dose of the study medication
- **Started treatment** –the very first dose of study medication
- **Restarted treatment** –a restart of the study medication after a temporary discontinuation
- **Other Specify** – none of the other types fit; you must specify the type of change in the "Other Type of Change" free-text field

Other Type of Change: If "Other Specify" has been selected as the "Type of Change", you must briefly specify the type of change in this free-text box. Note: you are not to enter anything in this field if you did not specify "Other Specify" in the previous field.

Reason for Change (select all that apply): All types of change (with the exception of "No change") require a "Reason for Change." More than one reason may apply. Use the following as a guide:

- **Lab safety assessment results** – A liver enzyme result 2.5 times normal, a doubling of creatinine, etc.
- **Allopurinol contraindicated** – subject is prescribed a medication for which allopurinol is contraindicated, such as amoxicillin
- **Off-label allopurinol treatment required** –subject diagnosed with gout that requires treatment

- **Pregnancy or breastfeeding** – two menstrual cycles are missed and pregnancy is suspected or confirmed
- **End-stage renal disease** – eGFR is less than 15
- **Per protocol change dose after 1st month** – subject has completed the 30-day initial dosing period
- **Change in eGFR** – reaching a threshold that dictates a change in study drug dosage, as per the protocol
- **Started treatment** – “Type of Change” is also Started treatment
- **Restarted treatment** – “Type of Change” is also Restarted treatment
- **Other Specify** – none of the other types fit; you must specify the reason for change in the “Other Reason for Change” free-text field

Other Reason for Change: If “Other Specify” has been selected as the “Reason for Change”, you must briefly specify the reason for change in this free-text box. Note: you are not to enter anything in this field if you did not specify “Other Specify” in the previous field.

Following are four examples demonstrating different scenarios you may encounter when completing the Study Medication Log.

EXAMPLES:

1. Visit 6 – Subject started study medication and took throughout the dosing period as expected.

The screenshot shows the 'Study Medication Log' interface. At the top, it displays 'Exposure (1/10)', 'Compliance (0/36)', and 'Compliance (0/2)'. Below this, there are instructions and a 'Save' button. The main section asks 'Has the subject permanently discontinued the study drug prior to this dosing period?' with a 'No' selection. A table lists medication events:

Start Date	Start Date Unknown	Stop Date	Stop Date Unknown	Dosage Dispensed by Pharmacy	Type of Change	Other Type of Change	Reason for Change (select all that apply)	Other Reason for Change
01-Dec-2015	Unknown	02-Jan-2016	Unknown	100 (mg/day)	Started treatment		Per protocol change dose after 1st month Change in eGFR Started treatment Restarted treatment	

Buttons for 'Add', 'Return to top', 'Save', and 'Exit' are visible at the bottom.

2. Visit 7 – Per protocol, dose increased and subject took the study medication throughout the dosing period as expected

The screenshot shows the 'Study Medication Log' interface. At the top, it displays 'Exposure (1/10)', 'Compliance (0/36)', and 'Compliance (0/2)'. Below this, there are instructions and a 'Save' button. The main section asks 'Has the subject permanently discontinued the study drug prior to this dosing period?' with a 'No' selection. A table lists medication events:

Start Date	Start Date Unknown	Stop Date	Stop Date Unknown	Dosage Dispensed by Pharmacy	Type of Change	Other Type of Change	Reason for Change (select all that apply)	Other Reason for Change
03-Jan-2016	Unknown	01-May-2016	Unknown	400 (mg/day)	Change in dosage		Per protocol change dose after 1st month Change in eGFR Started treatment Restarted treatment	

Buttons for 'Add', 'Return to top', 'Save', and 'Exit' are visible at the bottom.

3. Visit 8 – No change in dose and subject took the study medication throughout the dosing period as expected

Exposure (1/10) Compla... (0/38) Compla... (0/2) -- Select to Jump --

Title: Study Medication Log

Instructions: Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period.
The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Pages:

Has the subject permanently discontinued the study drug prior to this dosing period?:

Start Date	Start Date Unknown	Stop Date	Stop Date Unknown	Dosage Dispensed by Pharmacy	Type of Change	Other Type of Change	Reason for Change (select all that apply)	Other Reason for Change
02-May-2016	<input type="checkbox"/> Unknown	01-Sep-2016	<input type="checkbox"/> Unknown	400 (mg/day)	No change		Lab safety assessment results Aloprinol contraindicated Off-label aloprinol treatment required	

Return to top

4. Visit 9: Subject started the dosing period with no change, then had to stop taking the drug for several days due to an out of range lab result, then restarted treatment through the remainder of the dosing period

Exposure (1/10) Compla... (0/38) Compla... (0/2) -- Select to Jump --

Title: Study Medication Log

Instructions: Refer to the MOO for detailed instructions and examples. All dosages and discontinuations must be listed for the entire Dosing Period.
The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills.

Pages:

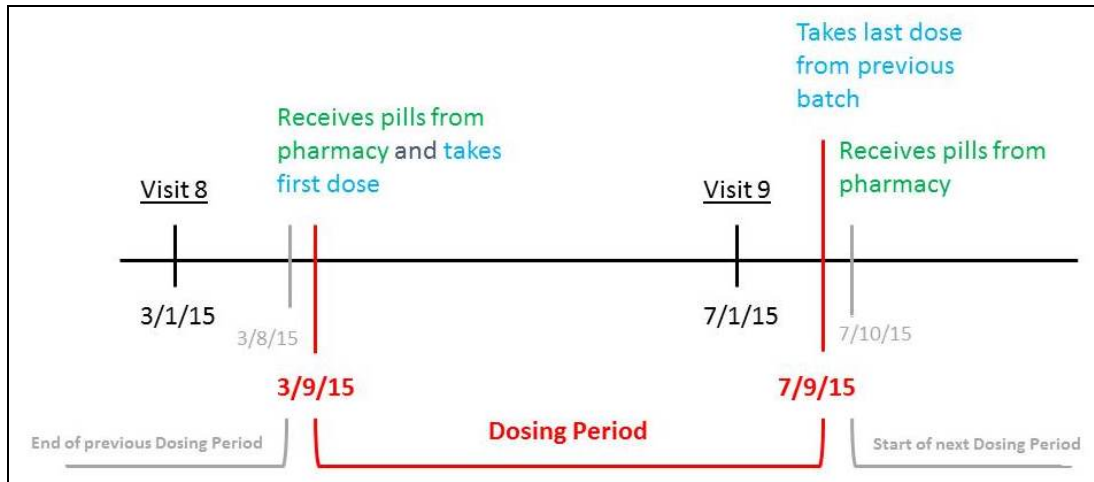
Has the subject permanently discontinued the study drug prior to this dosing period?:

Start Date	Start Date Unknown	Stop Date	Stop Date Unknown	Dosage Dispensed by Pharmacy	Type of Change	Other Type of Change	Reason for Change (select all that apply)	Other Reason for Change
02-Sep-2016	<input type="checkbox"/> Unknown	15-Sep-2016	<input type="checkbox"/> Unknown	400 (mg/day)	No change		Lab safety assessment results Aloprinol contraindicated Off-label aloprinol treatment required	
16-Sep-2016	<input type="checkbox"/> Unknown	01-Oct-2016	<input type="checkbox"/> Unknown	0 (mg/day)	Temporarily discontinued		Lab safety assessment results Aloprinol contraindicated Off-label aloprinol treatment required	<input checked="" type="checkbox"/>
02-Oct-2016	<input type="checkbox"/> Unknown	02-Jan-2017	<input type="checkbox"/> Unknown	400 (mg/day)	Restarted treatment		Per protocol change dose after 1st month Change in eGFR Started treatment Restarted treatment	<input checked="" type="checkbox"/>

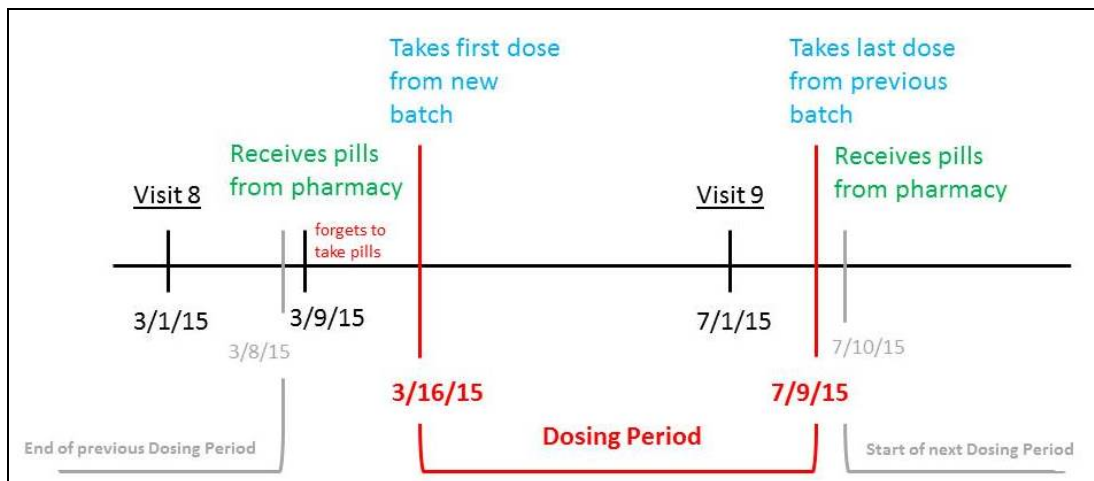
Return to top

NOTE: The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills after the next visit. Please refer to the following examples for further explanation.

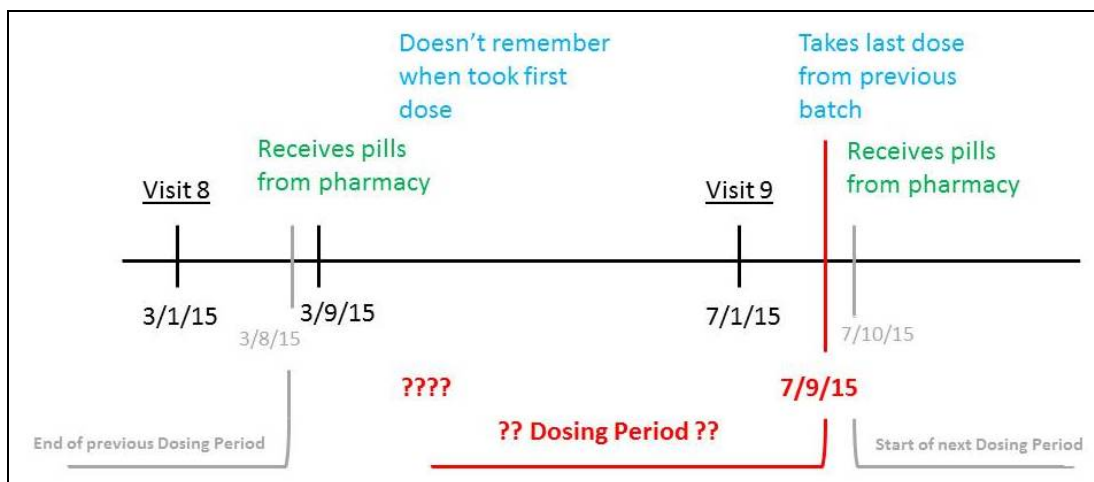
Example 1: Subject takes pills as expected



Example 2: Subject doesn't start taking pills until a few days after receiving them



Example 3: Subject can't remember when they start taking pills



Once all data entry is complete, click the "Save" button. If you have not completed a field or made a data entry error, a discrepancy will fire. Correct whatever needs to be fixed and click the "Save" button again. The next tab, Study Drug Exposure, becomes active.

The screenshot shows a web-based form titled "PERL_022_Study Drug Compl & Expo t1.34" with a subject ID of "0002TEST". The form includes a navigation bar with tabs for "Exposure (15/28)", "Complia...(0/38)", and "Complia...(0/2)", along with a "Select to Jump" dropdown. The main content area is titled "Study Drug Exposure" and contains instructions: "For the entire Dosing Period. The Dosing Period starts with the date the subject takes the first pill from the shipment received after the prior visit and ends with the date the subject takes the last pill from that shipment because they received a new shipment of pills." Below the instructions are "Save" and "Exit" buttons.

The form is divided into several sections:

- 1a. Date started using drug vials:** Includes a date input field and an "Unknown" checkbox.
- 1b. Date stopped using drug vials:** Includes a date input field and an "Unknown" checkbox.
- Difference in days:** A text input field, highlighted with a blue rounded rectangle and labeled "Calculated" on the left.
- 1c. Number of pills should have taken if there were no Discontinuations:** A text input field and an "Unknown" checkbox.
- 2. Number of pills instructed not to take:** A text input field.
- 3. Number of pills should have taken:** Includes a "Total number of pills instructed not to take:" field, a note "(by vial because the number can be different for each vial)", and four vial-specific input fields (A, B, C, D), each with a "Total number of pills should have taken:" field below them.
- 4. Number of pills dispensed:** Includes a "Total number of pills instructed not to take:" field, a note "(by vial because the number can be different for each vial)", and four vial-specific input fields (A, B, C, D), each with a "Total number of pills should have taken:" field below them.
- 5. Were pills returned in individual vials:** A dropdown menu with "(Select)" and an "Unknown" checkbox.
- 7. Select the reason Drug Compliance cannot be calculated at this visit:** A dropdown menu with "(Select)" and an "Unknown" checkbox.

At the bottom of the form are "Return to top", "Save", and "Exit" buttons.

NOTE: All calculated fields will calculate when you click the "Save" button.

1a. Date started using drug vials: Select the date the subject started taking pills from the new (or initial) batch received from the pharmacy. Ideally, this would be the day after they took the last pill from the previous batch of pills. This date will be the same as the **FIRST** Start Date on the Study Medication Log. If the subject cannot remember the date, or it is otherwise unknown, click the "Unknown" checkbox. Compliance cannot be calculated without this date; therefore, a reason must be selected in **7**.

1b. Date stopped using drug vials: Select the date the subject stopped taking the study medication for this dosing period. Ideally, this will be the day before the subject starts taking pills from the next batch of pills received from the pharmacy. This date will be the same as the **LAST** End Date on the Study Medication log. If the subject cannot remember the date, or it is otherwise unknown, click the "Unknown" checkbox. Compliance cannot be calculated without this date; therefore, a reason must be selected in **7**.

Difference in days: 1b minus 1a (CALCULATED).

1c. Number of pills subject should have taken during this dosing period: (Difference in days plus 1) times 4 (CALCULATED). If the Date started using drug vials and/or the Date stopped using drug vials are "Unknown", the number of pills the subject should have taken cannot be calculated. In that case, click the "Unknown" button. A text box will appear where you are to enter a brief explanation why you are unable to calculate the number of pills the subject should have taken. Compliance cannot be calculated without this information; therefore, a reason must be selected in **7**.

2. Number of pills instructed not to take: If the subject was instructed NOT to take any pills during this dosing period, enter the number, by vial. This does not include pills the subject may have forgotten to take or didn't take for some other reason – only those pills they were **instructed** not to take. These are required fields. If they were not instructed to not take any pills, then enter "0" (zero) for each vial. The total will be calculated.

3. Number of pills should have taken: 1c minus 2 (CALCULATED).

4. Number of pills dispensed: Enter the number of pills dispensed by the pharmacy for this dosing period, by vial. These are required fields. The total will be calculated.

The following examples are provided to give further guidance on completion of the CRF to this point:

EXAMPLE 1: After having labs at Visit 8 on 3/1/2015, the study drug prescription is faxed to the pharmacy and subject receives the pills from the pharmacy on 3/8/2015. Subject takes their first dose the next morning. Therefore, 3/9/2015 is the Start Date of the Dosing Period for the Visit 8 to Visit 9 time period. (NOTE: 3/8/2015 should be the end of the Dosing Period for the Visit 7 to Visit 8 time period.) Subject comes back 4 months later for Visit 9 on 7/1/2015

and has labs done again. A study drug prescription is faxed to the pharmacy and subject receives a new batch of pills from the pharmacy on 7/9/2015. The subject takes pills from the new batch the next morning, so the End Date of the Dosing Period (from Visit 8 to Visit 9) is 7/9/2015, when the subject took the last dose from the previous batch of pills. 3/9/2015 through and including 7/9/2015 is 123 days. 123 times 4 equals 492. That is the number of pills the subject SHOULD have taken during the dosing period if there were no discontinuations. Note that the dosing period from Visit 8 to Visit 9 is associated with Visit 9 in OpenClinica.

EXAMPLE 2: After having labs at Visit 8 on 3/1/2015, the study drug prescription is faxed to the pharmacy and subject receives the pills from the pharmacy on 3/8/2015. Subject, for whatever reason, doesn't take their first dose from the new batch until 3/16/2015 even though they stopped taking the previous dose when the new batch arrived. Therefore, 3/16/2015 is the Start Date of the Dosing Period for the Visit 8 to Visit 9 time period. (NOTE: 3/8/2015 should be the End Date of the Dosing Period for the Visit 7 to Visit 8 time period.) Subject comes back 4 months later for Visit 9 on 7/1/2015 and has labs done again. A study drug prescription is faxed to the pharmacy and subject receives a new batch of pills from the pharmacy on 7/9/2015. The subject takes pills from the new batch that evening, so the End Date of the Dosing Period (from Visit 8 to Visit 9) is 7/9/2015, when the subject took the last dose from the previous batch of pills. 3/16/2015 through and including 7/9/2015 is 116 days. 116 times 4 equals 464. That is the number of pills the subject SHOULD have taken during the dosing period if there were no discontinuations. Note that the dosing period from Visit 8 to Visit 9 is associated with Visit 9 in OpenClinica.

EXAMPLE 3: After having labs at Visit 8 on 3/1/2015, the study drug prescription is faxed to the pharmacy and subject receives the pills from the pharmacy on 3/8/2015. Subject cannot remember when they took the first dose from the new batch. Therefore, the Start Date of the Dosing Period is unknown for the Visit 8 to Visit 9 time period. (NOTE: 3/8/2015 should be the End Date of the Dosing Period for the Visit 7 to Visit 8 time period.) Subject comes back 4 months later for Visit 9 on 7/1/2015 and has labs done again. A study drug prescription is faxed to the pharmacy and subject receives a new batch of pills from the pharmacy on 7/9/2015. The subject takes pills from the new batch the next morning, so the End Date of the Dosing Period (from Visit 8 to Visit 9) is 7/9/2015, when the subject took the last dose from the previous batch of pills. Because the Start Date of the dosing period is unknown, the length of the dosing period is unknown; therefore, the number of pills the subject SHOULD have taken cannot be determined. Please try to impress upon your subjects the importance of recording start and stop dates. Note that the dosing period from Visit 8 to Visit 9 is associated with Visit 9 in OpenClinica.

5. Were pills returned in individual vials: Select whether the pills were returned in the 4 individual vials. Response selections include (this is a required field):

- **Yes** – if selected, 4 fields are displayed for you to enter how many pills were returned, by vial. The total will be calculated.

- **No** – if selected, a single field is displayed for you to enter the total number of pills taken (**A4b**.)
- **Pills not returned** – if selected, compliance cannot be calculated and a reason must be selected in **7**.

5. Were pills returned in individual vials:

Yes

Number of Pills Returned:
(by vial because the number can be different for each vial)

Vial A: 7

Vial B: 7

Vial C: 7

Vial D: 7

Total number of pills returned:

5. Were pills returned in individual vials:

No

Total number of pills returned:

28

5. Were pills returned in individual vials:

Pills not returned

7. Select the reason Drug Compliance cannot be calculated at this visit:

(Select)

6. Number of pills taken: Number of Pills Dispensed by vial or Total minus Number of Pills Returned by vial or Total (CALCULATED)

EXAMPLE: The pharmacy dispensed the 4 vials with 130 pills in each. The total number of pills dispensed is 520 (130 times 4). The subject returned the 4 vials with 7 pills left in each vial. The total number of pills returned is 28 (7 times 4). The total pills dispensed minus the total pills returned is 492 (520 minus 28); this represents the actual number of pills taken by the subject.

7. Select the reason Drug Compliance cannot be calculated at this visit:

(Select)

Subject did not return pills

Pills were thrown away

Pills were lost

Start date and/or Stop date unknown

Not applicable

Other

If the pills were not returned (**5.**), and/or the subject cannot remember when they started and/or stopped taking the pills (**1a.**, **1b.**), there is no way to calculate compliance. Be sure to select a reason in **7**. If you select "Other," briefly specify a reason in the "Other" field. If all information required to calculate compliance is entered, select "Not Applicable" in **7**. This is a required field.


Once all data entry is complete, click the "Save" button. If you have not completed a field or made a data entry error, a discrepancy will fire. Correct whatever needs to be fixed and click the "Save" button again. The next tab, Study Drug Exposure, becomes active.

Compliance is calculated using the number of pills reported taken from the 4 vials (6.) or the total number of pills taken, compared with the number of pills the subject should have taken (3.). If the participant is 100% compliant, the total number of pills taken should equal the total number of pills the subject SHOULD have taken during the dosing period. Note the compliance percentage (B1. or B2, depending on if the pills were returned in the 4 vials or not) and if necessary, take action to assist the subject in improving their adherence to taking the study medication. If pills were not returned or if there is some other reason compliance cannot be calculated, these fields will remain blank.


Your data has been saved. You can continue entering/editing data now or return at a later time.

Exposure (6/8) Compla...(9/17) **Compla...(1/2)** -- Select to Jump --


Title: % Compliant Calculation

Page: Mark CRF Complete **Save** **Exit** 

B1. Percent Compliant
(if total pills taken reported by the 4 individual vials)



B2. Percent Compliant
(if vials not returned and total pills taken reported as a total only)

[Return to top](#) Mark CRF Complete **Save** **Exit** 

Please note the compliance calculation will not appear until you click the "Save" button on the Compliance Calculation tab. Once you click "Save", the final tab appears where you'll find a reminder to upload your source document in the Source Document event. You can now return to any of the previous tabs to review the subject's compliance as well as pill counts and calculations.

Complia...(0/38) Complia...(0/2) SourceD...(0/1) -- Select to Jump --

Title: Upload Your Form 022 Source Document

Instructions: **Don't forget to upload your source document!**

- Go to the Source Document event
- Open the PERL_022_Source Documents form
- Upload your source document to the appropriate visit field

You can now return to the Compliance tab to review subject's compliance and if you wish, the Exposure tab to review pill counts and calculations.

Page: Mark CRF Complete

Confirm form is complete and source document uploaded.

Return to top Mark CRF Complete

When you are ready to confirm the form is complete and source document is uploaded, click the final confirmation checkbox, click the "Mark CRF Complete" checkbox, then click the "Save" button. A message will appear stating data entry is finalized but you can still edit data if necessary. Click the "OK" button then click the "Exit" button and the form will close.

Discrepancies – some reminders:

The process order is important so you can avoid duplicate discrepancies:

1. Enter data
2. Save
3. Discrepancies fire
4. Make corrections to data incorrectly entered (do not enter any notes by clicking on a **gray** flag)
5. Save again (you'll be taken to the next tab)
6. Return to tab
7. Address any red-flagged discrepancies by clicking on the red flag and explaining, making sure you change the status to "Resolution Proposed"

On this form ONLY, you can ignore any discrepancies that fire with the following message:

<meaningless variable name> is empty

FORM 023i-INITIAL COMPLICATIONS QUESTIONNAIRE

This form is to be completed for all **randomized** subjects at their **next study visit**, with the exception of those who have withdrawn consent, are lost to follow-up, or are deceased. **If a subject has already completed Visit 17, the site should attempt to contact the**

subject and obtain this data via telephone (if allowed in the informed consent). If a subject's next visit is Visit 17, and the visit occurs after July 1, 2017, the site should attempt to contact the subject and obtain this data via telephone (if allowed in the informed consent). If unable to contact the subject, this form **will** be completed at the time of the visit. Questions should be answered as if the form is being completed at screening.

When scheduling the event for data entry, use the same date that you use for the visit in which the form is being completed. If the subject has already completed the study, use the same date as when the Visit 17 occurred.

A1. Enter the date the questionnaire is being completed.

A2. through A8. Select "Yes", "No" or "Unknown" in response to each event or condition considering if it FIRST occurred PRIOR to PERL Visit 1. If "Yes" is selected, please enter the subject's age when the event or condition FIRST occurred.

B1. Select the statement that best reflects the subject's current health status.

C1. Has the subject ever been diagnosed with diabetic retinopathy PRIOR to PERL Visit 1. Selections are "Yes", "No" or "Unknown." If "Yes" is selected, answer the additional "Yes/No" questions (C2a-c and C3).

C4. Select the month and year of the subject's last dilated eye exam by an eye specialist PRIOR to PERL Visit 1 or check the "Unknown" checkbox.

D1. – D2. Answer each question considering whether each event or condition FIRST occurred PRIOR to PERL Visit 1.

D3. Through D17. Answer each of these question as they pertain to the subject **CURRENT HEALTH**.

E1. Select the subject's highest level of education PRIOR to PERL Visit 1.

FORM 023F-FOLLOW-UP COMPLICATIONS QUESTIONNAIRE

This form is to be completed for all **randomized** subjects at **Visit 17**. If a subject has completed the study, an attempt should be made to contact the subject and complete this form via telephone (if the informed consent allows for this).

A1. Select "Yes" or "No" in answer to the lead-in question. If the Initial Complications form has not been completed, EXIT THIS FORM and complete the PERL_023I_Initial_Complication Questionnaire.

B1. Select the statement that best reflects the subject's current health status.

D3. through D12. Answer each question considering the subject's **current health** status.

FORM 025-UNSCHEDULED VISIT REASON

An Unscheduled Visit is completed anytime the need arises for a subject to return to the clinic outside of the regular Visit Schedule. This could be due to required follow up for an adverse event, a missed/repeat procedure or to repeat a lab value.

The forms associated Unscheduled Visits are:

- 006 – Blood Pressure and Measurements
- 007 – Physical Examination
- 008 – Local Laboratory Results
- 009 – ECG Report
- 010 – Central Lab Specimen Collection
- 011 – Skin Assessment
- 019 – iGFR Procedures Form
- 025 – Unscheduled Visit Reason

Complete only the form(s) related to the specific reason the unscheduled visit has been completed.

Form 025 is to be completed for every Unscheduled Visit to document the reason for the visit.

A1. Select the reason for the Unscheduled Visit. If "Other" is selected, be sure to specify the reason in the free text field that appears.

If "iGFR repeat or reattempt" is selected (Complete Forms 006 and 019):

A1a. Select the visit where the iGFR procedure was performed or attempted that this procedure is to replace.

A1b. Select the reason the iGFR is being repeated or reattempted.

A1b1. If "Invalid R2", select which samples were tested. If backup samples were not tested, specify why.

A1b2. If "Could not be completed", select the reason why. **NOTE:** If "Other" is selected, specific reason is not required as it is documented on Form 019.

If "Safety Check" is selected (Complete form(s) related to the Safety Check(s)):

A1c. Select all Safety Checks performed (a safety check is defined as any protocol-mandated repeat of an out-of-range lab value).

A1d. Select the visit where something occurred prompting the Safety Check(s). **NOTE:** Select "None" if the Safety Check is not related to a visit.

A1d1. If "Unscheduled Visit" is selected, select which number.

FORM 026-HISTORICAL eGFR SLOPE

This form is to be completed for **all randomized** subjects that qualified by albuminuria (ACR or AER) at screening. If the subject was qualified by eGFR slope, and information and is already entered on Form 016 (ACR/AER Screening), please **DO NOT** complete this form. To verify if you should be completing this form, answer the lead-in question "Was the subject qualified for the study using eGFR slope as an eligibility criteria as indicated on PERL_016_ACR/AER Screening, selection of A1c?" If the answer is "Yes," nothing else should be completed. If the answer is "No," proceed with completing the rest of the form.

Enter the eGFR Slope Calculation Result. An EXCEL-based eGFR and slope calculator is available on the PERL website, in the Coordinator Dropbox, to assist with calculating eGFRs and slope.

eGFR slope will be calculated to align with the intent of the protocol. If sites have entered more eGFR values than required to meet the intent of the protocol, they will be asked to recalculate the slope using only the values needed. Additional eGFR values entered but not required for the slope calculation can remain on the form.

Enter a **minimum** of THREE eGFR dates and values. The most recent is to be from screening (using the local lab creatinine value). The oldest value is the value that is closest to 3 years that is **GREATER** or **EQUAL** to three years ago, but no more than 5 years ago. You must go back far enough to have at least THREE values. All the other value(s) between the most recent value and the oldest value must be entered. If three values are not available within the 5 years preceding study participation, enter those that are available.

FORM 035-FINAL STATUS

A1. Enter the date of last visit, date of withdrawal, date participant was deemed ineligible, or date of death.

A2. Enter the reason the participant will not be continuing in the study at this site.

- **Completed Study:** Defined as the participant completed Visit 17. This is regardless of whether they discontinued study medication early or whether they completed all study visits.
- **Transferred to another site:** If transferred, enter the site # and new participant ID.
- **Other:** If this is a response, complete reason for termination.

Note: If the Final Status is Death - The date of death must be reported in A1. (Cause of death MUST be captured as an SAE.)

FORM 040-PROTOCOL DEVIATION LOG

This form is a running log and can be completed at any time during the study.

- For each new deviation, click on the "ADD" button.
- If a row was added inadvertently, click on the "X" button at the end of the row to remove it. If the form has already been saved you cannot delete the new row so ensure that all responses are blank if the row was not intended to be added.

Which Visit?	Deviation	If Other deviation, specify	If Study Procedure, which one	Reason	Additional Comments
Select which visit the deviation is related to. If it is not visit related such as medication error, select "Not visit related"	Choose one type of deviation. If not listed choose other and specify in the next column	Use only if Deviation was not listed.	Use only if Deviation was Study Procedure not completed or completed incorrectly	Select one reason for deviation. If more than one, record additional reasons in comment field.	This column may remain blank. Record only relevant info to further explain

FORM 045-SERIOUS ADVERSE EVENT

Please refer to Chapter 8 of the MOO for additional instructions on reporting an SAE.

This form is for all adverse events that meet the definition of serious. All non-serious adverse events should be recorded on Form 20 AE log.

NOTE: Once you save this form for the first time the SAE reporting process will begin by generating an email to the SAE committee and creating a draft narrative report.

The following fields are required in order to save the initial SAE form, please have this information available at the time of the initial report:

- A3. Diagnosis
- A6. Start Date

A2: Criteria: All relevant reasons for eligibility as an SAE should be checked. If "Other" is marked, a comment box appears to enter the criteria.

A3. AE Diagnosis: Please refer to the Adverse Event log 020 drop down list for consistent terminology whenever possible. This should be only 1-3 words, and indicate the overarching diagnosis of the event; this is not a summary of the entire event (a full summary is included below), and only **ONE** diagnosis should be indicated. If more than one diagnosis is made, a separate SAE event should be completed for each.

A4. Description: All relevant diagnostic and laboratory results should be reported in this section, as well as any relevant details regarding the event timeline. This should read as a full narrative of the event, with minimal abbreviations (except commonly used and accepted medical abbreviations, such as: ECG, ER, mg, CT, MR, etc.).

A5. Treatment: Include all medications, physical therapy, surgical and medical treatments.

A6. Start Date: Entered in DD-MMM-YYYY format. Start time is entered in 00:00 format 24 hr clock. If start time is unknown, mark "Unknown."

A7. Outcome: Indicate the status of SAE outcome: Recovered without sequelae would indicate that the participant recovered without residual issues related to the SAE. Recovered with sequelae would then be a choice if a participant is recovered but has ongoing issues related to the SAE.

A7a. End Date: Entered in DD-MMM-YYYY format. Start time is entered in 00:00 format using the 24 hr clock. If start time is unknown, mark "Unknown."

A8. Severity: Indicate the severity grade of the AE. For accurate grading, refer to the MOO.

A9. Causality: Indicate relationship to allopurinol/placebo, refer to SAE/AE guidelines for definitions of: Definite, Probable, Possible, Not Related (none), and Not Assessable (insufficient data).

A10. Action taken due to this event: Indicate action taken in terms of the allopurinol/placebo. This is not to be confused with "A5: Treatment". A discontinuation of allopurinol/placebo would occur if the hospital physicians and/or PI felt they could not rule out a relationship to allopurinol/placebo. A reduction of allopurinol/placebo would also be used in cases where the causality is: Definite, Probable or Possible. Please note, if a subject experienced a SAE that is not related, the subject could still miss doses of their study medication. For example, a participant broke his leg and was admitted to the hospital. He forgot his medication and missed 3 doses. In this instance the cause is: *not related*, the action taken is *allopurinol/placebo interrupted*, and the participant remains on allopurinol/placebo. The missed doses will be captured in the subject's compliance log. If the causality is not related, and the subject continues to take their study medication throughout the event as directed, the action taken is *no action taken*.

A10a. If allopurinol/placebo discontinued or reduced, did SAE abate: This question will only appear if A10 is indicated as "*study drug/placebo discontinued or reduced*".

A10b. If allopurinol/placebo was discontinued indicate date of last dose: This question will only appear if A10 is indicated as "*Discontinued allopurinol/placebo*".

A10c. If allopurinol/placebo dose was reduced indicate date reduced was instituted and date full dose resumed: This question will only appear if A10 is indicated as "*allopurinol/placebo dose reduced*".

A10d. If allopurinol/placebo dose was interrupted indicate stop/start dates: This question will only appear if A10 is indicated as "*allopurinol/placebo interrupted*".

MISSED VISITS:

A missed visit is defined as a subject being more than half way to the next visit window (in which case the subject advances to the next visit), and thus the visit is not performed. If a subject completely misses a protocol-mandated study visit, the following process must be used:

1. Schedule the visit
2. Change the status of the visit to "Skipped"
3. Enter a protocol deviation in Form 040

The details as to why the visit was missed should be clearly documented in the subject binder, and a Protocol Deviation Form 040 must be completed as described above.

DISCREPANCY COMPLETION

Discrepancies – some reminders

The process order is important so you can avoid duplicate discrepancies:

1. Enter data
2. Save
3. Discrepancies fire
4. Make corrections to data incorrectly entered (do not enter any notes by clicking on a **gray** flag)
5. Save again (you'll be taken to the next tab or the form will close)
6. Return to tab (or reopen form)
7. Address any red-flagged discrepancies by clicking on the red flag and explaining, making sure you change the status to "Resolution Proposed"

Chapter 8

Adverse and Serious Adverse Events

8.1. Adverse Event (AE) / Serious Adverse Event (SAE)

8.1.1 Definitions:

Adverse Event (AE) is any untoward medical occurrence in a participant, regardless of its relationship to study treatment.

Serious Adverse Event (SAE) is any untoward medical occurrence that results in:

- Death
- A life-threatening adverse event
- Requires Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that do not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the research participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2. Adverse Event Reporting

All AE's that occur from the time the consent is signed at Visit 1 to 30 days after the final visit (Visit 17) must be reported. Information concerning the AE should be captured on Worksheet #20 and then submitted to the Data Coordinating Center (DCC) in Open Clinica, on eCRF 20. The clinic must report them at the time they become aware of them (within 72 hours of the site's knowledge of the event), or at the next scheduled visit if the participant doesn't report them until that time. The AE/SAE log should be updated with each event and kept in the front of the participant's research file. If an event has been reported as "ongoing", upon resolution it should be updated on eCRF 20 and the AE/SAE log.

Pre-existing conditions (conditions that were known to be present *prior to* ICF signing or are identified during the screening procedures at Visit 1) will not be considered or recorded as AEs unless the condition worsens in intensity or frequency after Visit 1. Likewise, continuing AEs will not be reported as AEs at subsequent visits unless they increase in severity or frequency between visits or they result in criteria that qualify the AE for submission as a SAE. Summaries of AEs tabulated by each clinical center will be provided to the Data Safety Monitoring Board (DSMB) by the Data Coordinating Center on a quarterly basis. The DSMB will decide on actions needed, if any, for the study group.

The fact that the study staff is masked to treatment assignment will insure that AEs are ascertained in an unbiased manner using the same standardized methodology for all participants.

8.3. Criteria to define the *Severity of an Adverse Event*:

The severity of the Adverse Event should be defined by using the following criteria:

- **mild** – events are usually transient, requiring no special treatment and do not interfere with the patient's daily activities. Mild events are easily tolerated.
- **moderate** – events traditionally introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures. Moderate events may cause some interference with daily activities.
- **severe** – events interrupt a patient's normal daily activities and traditionally require intensive therapeutic intervention. Severe events are usually incapacitating.

8.4. Criteria to Define *Expected/Unexpected Events*:

Expected is a possible expected adverse drug side effect as outlined in the current drug insert, e.g. patients that develop a cough from ramipril (or other ACEi) or out of range blood work from allopurinol.

Unexpected is an unexpected adverse drug side effect, the specificity or severity of which is not outlined in the current drug insert.

8.5. Criteria to define the study medication relationship: (*causality*)

A causality assessment is complex, because the causal relationship is not always obvious. It is largely subjective and requires the experience of the investigator/physician. The relationship between study participation and/or study meds and an adverse event must be determined by the study physician according to the following criteria:

The causal relationship between the administration of a study procedure and/or the study medication and the AE are defined as follows:

- **Not related**– the adverse event is definitely not associated with the study OR study medication. Usually a concomitant illness is not study drug related.
- **Possibly related**– (a) the adverse event follows a reasonable temporal sequence from medication administration and (b) could have been produced by the participant's clinical state or other modes of therapy administered to the patient.
- **Probably related** – (a) the adverse event follows a reasonable temporal sequence from the medication administration; (b) abates upon discontinuation of the medication; and (c) cannot be reasonably explained by known characteristics of the study participant's clinical state. This indicates that the event was likely related to the study medication, but cannot be determined with definite certainty.
- **Definitely related** – the adverse event is definitely associated with the study medication administered, as determined by the study physician and/or the Drug Monitoring Committee.
- **Insufficient data/Not accessible** – there is insufficient data available to assess causality.

8.6 SAE Reporting

Information regarding all **SAEs**, as defined previously, should be collected on Worksheet 45 and reported on the SAE eCRF (Form 45). SAE's require expedited safety event notification **within 72 hours of occurrence, or awareness by the clinical center**, to the DCC.

The DCC will promptly notify the study PIs and Medical Safety Monitor (MSM) who may convene a Drug Monitoring Committee (DMC) conference call to acquire further information about the event and take appropriate actions concerning the study medication.

An independent physician, Massimo Pietropaolo, MD, Associate Director, Baylor College of Medicine, who is not directly involved in the study, will serve as the MSM and will review all SAEs promptly after being reported in the database by the clinical sites. Based on the clinical site report and any additional input from the DMC, the MSM will prepare a preliminary SAE narrative report (in cases where the SAE is not resolved) for each SAE which will be distributed to the PIs, NIDDK Program Director, DSMB Chair, clinical site director, and appropriate DCC staff. The MSM may enter queries for the site to respond to during their review of the SAE. It is important that the site responds to these **as soon as possible**. Once the SAE is resolved, a final SAE narrative report is generated by the MSM. This report will be sent to the clinical site director to review for accuracy and completeness. Following review by the clinical site director, the MSM will send the final SAE narrative report to the PIs, NIDDK Program Director, DSMB Chair, clinical site director, and appropriate DCC staff. All SAE narrative reports, both preliminary and final, will be reviewed by the DSMB during their regularly scheduled meetings or on an expedited basis as determined by the NIDDK Program Director, who will solicit the input of the Chair of the DSMB as needed. The FDA definitions and requirements for expedited reporting will be used to determine if any individual SAE warrants notification to the FDA and to the IRBs of all participating PERL clinical sites.

The clinical site at which the SAE occurred is responsible for expedited reporting of the SAE to their respective IRB. Each site is responsible to report all AE's to their IRB according to its AE reporting policy and procedures.

On behalf of the NIDDK, the DCC will submit an expedited safety report to the FDA for all serious unexpected suspected adverse reactions (SUSARs) *i.e.* when the SAE is unexpected and may be related to the study drug based on evidence of causality. This report will include information on frequency of similar events along with a narrative of similar events to provide context for the individual report. Copies of the expedited safety report will be provided to the PIs, NIDDK, DSMB, and site investigators.

8.6.1 SAE Reporting Procedure

1. Site completes SAE Worksheet #45 and submits Form 045 eCRF in Open Clinica within 72 hours of occurrence (including the upload of any related source documents/discharge summaries/etc.) or awareness by the clinic of the event.
2. Medical Safety Monitor (MSM) and PI's receive an email notification of new SAE.
3. MSM logs into the PERL SAE summary page and reviews the narrative for completeness & consistency.
4. If there is any additional information needed the MSM will query the clinical site for any changes/clarification by typing a question into the Comment box of the SAE narrative and changing the status to "Monitor Query". This will generate an email to the site.

6. The site will address the queries then change the status in narrative to "Site Response", and return it to the MSM. This must be done as soon as possible. **Any updates to the SAE (resolution, treatment, diagnostic test results) should be recorded on the SAE eCRF (Form 45) and saved.** This will update the narrative automatically within 24 hours.
7. The Site Director will receive an email requesting their review of the SAE as it appears in the narrative system. Additional changes should be made in OC at this time, if warranted, and an email sent to the DCC at perlstudy-pm@umich.edu when the SAE is completed to the Site Director's satisfaction.
8. Once all queries are addressed and the SAE eCRF is complete, the MSM finalizes the SAE narrative and the DCC will QC it. The status is then changed to "DSMB/NIH Preliminary if the SAE is not yet resolved, or DSMB/NIH Final if the SAE is resolved. An email is sent to the PI's clinical site, DCC, DSMB Chair, and NIH, notifying them of availability of completed narrative.
9. The PI then signs narrative & coordinator uploads the final narrative into the SAE eCRF Form 45.
10. The Coordinator marks SAE eCRF complete & PI signs the SAE event in OpenClinica

8.7 Abnormal laboratory values

Safety levels have been set for flagging **central** lab test results. When these levels are reached or exceeded, the Central Biochemistry Laboratory (CBL) will notify the DCC that an abnormal result has been received. The follow-up procedures that must be followed by the clinical sites when any abnormal results are received are described in the Side Effect Treatment Procedure (Session 8.9).

PATIENT SAFETY THRESHOLDS

LAB TEST	ALERT	ACTION TO BE TAKEN	AE
ALT	Doubling over baseline AND 2.5x above the upper limits of normal	Measurement must be repeated within 2 weeks, and if confirmed to be elevated, discontinue the study drug and, IF within 8 weeks of RASB initiation, also discontinue RASB. ALT should be repeated 4 weeks after drug discontinuation, and complete report sent to the DMC once this result is available to determine further action.	AE should be completed if ALT is confirmed to be elevated.
WBC	WBC <3500 x 10⁶/L	Measurement must be repeated with differential within one week, and if value confirmed to be <3500 x 10 ⁶ /L, temporarily discontinue the study drug. Report to the DMC. File an AE if indicated. Repeat WBC 2 weeks after drug	AE should be completed if WBC < 2500 x 10⁶/L and/or ANC <1000 x 10⁶/L

		discontinuation. If WBC recovers, consider re-challenging and repeating WBC 2 weeks after drug re-introduction.	
	WBC $\geq 15,000 \times 10^6/L$	Evaluate for possible infection. If there are signs of infection, required repeat within 24 hours and refer to PCP for evaluation. Complete AE. In the absence of infection, repeat measurement within 2 weeks; if leukocytosis is confirmed, and there is no evidence of infection, discuss with patient's provider and consider hematology referral. Complete AE.	AE should be completed for sustained elevated WBC $\geq 15,000 \times 10^6/L$
Platelets	$< 100 \times 10^9/L$	Measurement must be repeated within 1 week. If confirmed, discuss with subject's provider and consider a hematology referral. Report to DMC. If sustained platelets counts $< 100 \times 10^9/L$. Complete AE.	AE should be completed for sustained platelets counts $< 100 \times 10^9/L$
	$\geq 600 \times 10^9/L$	Measurement must be repeated within 1 week. If confirmed, discuss with patient's provider and consider a hematology referral. Complete AE.	AE should be completed for sustained platelets counts $\geq 600 \times 10^9/L$
Potassium	$\geq 6.0 \text{ mmol/L}$	Measurement must be repeated ASAP (no later than within 24 hours), and if confirmed elevated $\geq 6.0 \text{ mmol/L}$, RASB should be immediately discontinued and AE completed.	AE should be completed for confirmed potassium $> 6.0 \text{ mmol/L}$.
	$\geq 7.0 \text{ mmol/L}$	If potassium $\geq 7 \text{ mmol/L}$, this is a medical emergency . Send study participant to nearest Emergency Department or Urgent Care Center for immediate assessment and treatment, including ECG and required repeat potassium measurement ASAP (on the same day). If ECG abnormality is consistent with hyperkalemia (e.g. peaked T waves) OR confirmation of potassium $> 7.0 \text{ mmol/L}$, discontinue RASB and patient should be immediately treated for hyperkalemia. Complete an SAE.	An SAE should be completed for confirmed potassium $> 7.0 \text{ mmol/L}$.
Hemoglobin	A decrease of 2 g/dL from baseline	Measurement must be repeated (time of repeat at Investigator's discretion) and if confirmed, assess possible	AE should be completed for confirmed

		causes. If confirmed, report to the DMC. Complete AE.	hemoglobin decrease of 2 g/dL over baseline
Serum Creatinine	Increase by 25% or more from baseline within 3 months of introduction of RASB	Measurement must be repeated within 2 weeks. If confirmed, reduce RASB dose by half, and complete AE. Repeat creatinine within 2 weeks and if creatinine does not improve after drug dose reduction, consider discontinuing RASB. Report to DMC.	AE should be completed if SCr confirmed to be >25% increased over baseline
	Doubling from baseline OR at any one year interval	Measurement must be repeated within 2 weeks. If confirmed, Report to the DMC. If this is an acute event and creatinine later improves, it should be reported as an AE. If this is diabetic nephropathy progression and there is no improvement, the subject has reached a secondary study end-point .	AE should be completed if this is an acute event and creatinine later improves.
eGFR	20% or more reduction in 1 year, at any one year interval	Measurement must be repeated within 2 weeks. If decrease confirmed at $\geq 20\%$ per year, refer to nephrologist. Report to DMC and complete AE reporting	AE should be reported if $\geq 20\%$ decline confirmed
	≤ 15 ml/min/1.73m²	Measurement must be repeated within 1 week. If confirmed, patient should discontinue study medication and the event should be reported to DMC. If this is an acute event and eGFR later improves, report as an AE. If this is diabetic nephropathy progression and there is no improvement, the patient reached a primary study end-point .	AE should be reported if this is an acute event and eGFR later improves
Eosinophils count	$\geq 1.0 \times 10^9/L$ Eosinophil count should be absolute, not % alone. If only % is reported and is elevated a complete differential should be done and the absolute count determined.	Measurement must be repeated within 1 week. If eosinophilia not present prior to study drug AND/OR it is $> 1.5 \times 10^9/L$, discontinue the study drug. Also consider discontinuing RASB IF patient has rash, fever, leukocytosis or any signs of organ damage. Report to the DMC. Complete AE (or SAE). Repeat Eosinophils 1 week after drug(s) discontinuation.	AE (or SAE if in association with organ damage) should be completed for sustained eosinophil count $\geq 1.0 \times 10^9/L$

		<p>If eosinophil counts normalize ($<1.0 \times 10^9/L$), and patient had no other signs of organ dysfunction, consider re-challenging with study drug and repeating eosinophils 2 weeks after re-introduction of study drug.</p> <p>If eosinophils became abnormal with re-challenge, discuss further action with DMC</p>	
OTHER	Any other laboratory abnormalities requiring intervention or change in management.	<p>Any other abnormal lab results should come to the attention of the site MD. If there is a question about the abnormality being an AE, the MD should contact the Medical Monitor (via the DCC) to make a determination.</p>	Medical Monitor to make a decision if an abnormal laboratory results meet criteria for AE reporting.
Hypotension	Hypotension accompanied by clinical symptoms (i.e.) dizziness, fainting	<p>RASB should be held until symptoms abate and reintroduced at $\frac{1}{2}$ dose. If patient on other antihypertensive agents, these should be the first to be discontinued or have their doses reduced. If symptoms recur on $\frac{1}{2}$ dose of RASB the drug should be discontinued and a DMC conference call should be convened. AE or SAE should be completed.</p>	AE should be completed for hypotension due to RASB
Hypertension	Hypertension (SBP $>140/90$ mmHg) accompanied by clinical manifestations (i.e.) CHF, severe headache, blurred vision, hypertensive crisis such as seizures, microangiopathy, deteriorated renal function, papilledema or additional evidence of intracranial hypertension.	<p>If BP found to be elevated ($>140/90$ mmHg on three different occasions (3 separate study visits), the dose of existing non-RAS antagonists antihypertensive drugs will be maximized, followed, if necessary, by the introduction of antihypertensive drugs of a different class. If the goal of BP $\leq 140/90$ mmHg is not achieved with these drugs within one month, a DMC call will be convened.</p> <p>Hypertensive Crisis: Patient should be admitted and treated in hospital. AE or SAE should be completed.</p>	AE (or SAE) should be completed

NOTE: It is the responsibility of the site coordinator, site physician, and site director to monitor and manage abnormal LOCAL lab results.

8.8 SAE Notifications

The clinical site at which the SAE occurred is responsible for reporting of the SAE to their respective IRB, according to local IRB regulations.

8.9 Side Effects Treatment Procedures

Criteria to withhold or discontinue (temporary or permanent) study medication – See Protocol Section 5.5.1 Discontinuation of study drug

- If a participant's study medication (allopurinol/placebo, or RAS blocker) is discontinued, whether it is at the participant's request, a non-PERL physician's advice, or a PERL physician's decision, the date and reasons for the discontinuation should be entered in the Study Medication Discontinuation Log and the DCC should be notified. The DCC will initiate a DMC e-mail. In more complex cases, a conference call to discuss the current situation will be scheduled by the DCC. The Study Drug Compliance and Exposure Log (eCRF #22) should be updated and the Data Coordinating Center notified when the patient **resumes** the study medication. AE Worksheet 20 and eCRF 20 should be completed, and Worksheet 45 and eCRF 45 if event qualifies as an SAE.
- The participant should be told that the DMC exists, that their situation will be discussed, and the best course of action will come as a recommendation from that Committee. The participant should be reassured that their safety comes first, above and beyond all study requirements, and that the plan of action will be determined with that priority.
- Document changes in the RAS Blockers or other anti-hypertensive drugs in RASB/Concomitant Medication Log #12/13 and eCRF #12/13. Update the RASB/Medication Log, the Concomitant Medication Log, and the DSMB Log and keep in the front of the participant's research file.

8.9.1 Side effects specific to allopurinol

1. Gout attacks

Clinical sites will be blinded to serum uric acid values. However, they will be notified by the DCC if these exceed 12 mg/dl in order to prevent gout attacks. If the uric acid level exceeds 12mg/dl and there are no gout symptoms study medications should be continued and acute causes of uric acid elevations such as dietary excesses, dehydration or acute increase in renal dysfunction should be sought and, if possible reversed. The uric acid level should be rechecked within 2 weeks. If there were no acute events or if acute causes are reversed and the uric acid level is still above 12 mg/dl, study medication should be stopped and the patient placed on open label allopurinol at the appropriate dose for their renal function. Study blind need not be broken. If the acute events are not yet reversed a Drug Monitoring Committee meeting should be held as soon as possible.

If gout is diagnosed, open-label treatment with allopurinol may be indicated after resolution of the acute attack, to prevent subsequent attacks acute gout attacks. This needs to be discussed with the study participant provider (PCC, endocrinologist, nephrologist,

rheumatologist, etc). In such case, the study drug will be discontinued and the open-label allopurinol will be titrated with the goal of bringing and keeping the serum uric acid level below 7.0 mg/dl. Participants will continue to be followed according to the study protocol and will remain in their blind randomization group for the purpose of data analysis.

The Study Drug Compliance & Exposure WS #22, RASB Medication Log #12, and Concomitant Medication Log #13 should be updated and completed to document all changes in medication. If necessary, eCRF # 40 should be completed to document any associated protocol deviations.

AE Worksheet 20 and eCRF Form 20 should be completed, along with Worksheet 45 and eCRF Form 45 if event qualifies as an SAE. Both of these forms will capture any discontinuation in study drug.

8.9.2 Side effects common to allopurinol and RAS Blockers.

1. Allergy and skin reactions

If participant develops a rash, hives, or any other acute skin changes, **stop the study drug and RASB immediately**, and follow the procedures outlined in paragraphs two and three of Section 8.9 above.

2. Angioedema

This side effect usually occurs within 48 hours (but not greater than 3 weeks) of taking the first dose of a medication. If this occurs, **stop the study medication and/or RAS Blocker immediately**, and follow the procedures outlined in paragraphs two and three of Section 8.9 above. At this point a DMC conference call will be convened to discuss the options.

3. Hepatic Toxicity

Liver enzyme tests (ALT) will be done at each visit except Visit 2 and Visit 5. If the ALT doubles over the baseline value AND it is 2.5X above the upper limits of normal, the measurement will be repeated within 2 weeks. If values are confirmed to be elevated, the study drug will be discontinued and if within 8 weeks of RASB initiation, also, ~~and~~ RAS Blocker will be discontinued. ALT should be repeated 4 weeks after drug(s) discontinuation, and a complete report sent to the DMC once this result is available to determine further action. If the study medication is discontinued, follow the procedures outlined in paragraphs two and three of 8.9.

4. Leukopenia

A WBC will be done at each visit except Visit 2 and Visit 5. If the WBC is < 3500, the test will be repeated within 1 week and if the value is confirmed to be <3500, the study drug will be temporarily discontinued. Report to DMC. Complete an AE if WBC < 2500 or ANC <1000. Repeat WBC 2 weeks after drug discontinuation. If WBC recovers, consider re-challenging and repeat WBC 2 weeks after drug re-introduction. If the study drug is discontinued, follow the procedures outlined in paragraphs two and three of 8.9.

If WBC \geq 15,000, evaluate for possible infection. If there are signs of infection, repeat WBC within 24 hours and refer to PCP for evaluation. Complete an AE. In the absence of infection, repeat measurement within 2 weeks; if leukocytosis is confirmed, discuss with patient's provider and consider hematology referral. Complete AE.

5. Pregnancy

The study drug (allopurinol/placebo) and the RASB must NOT be taken while a participant is pregnant or breastfeeding. If a participant becomes pregnant, **discontinue the study drug and RASB immediately**. Although the iohexol GFR cannot be done during pregnancy, ALL other procedures for the respective visits should be completed. The Clinic should submit an AE form and update it as "resolved" when the pregnancy is completed. If the participant is going to breastfeed the study drug should be held until breastfeeding has ceased.

If the participant decides to **plan** a pregnancy or start breastfeeding, the study medication and RAS Blocker must be discontinued as soon as the participant ceases using birth control. If the study drug is discontinued, follow the procedures outlined in paragraphs two and three of 8.9.

6. Breastfeeding

If participant is committed to breastfeeding, the study medication and RAS Blocker **cannot** be resumed until breastfeeding has been discontinued.

8.9.3 Side effects specific to RAS Blockers

1. Hyperkalemia

Hyperkalemia is defined as any value for serum potassium (K^+) that is elevated above normal (approximately **3.5 - 5.5 mEq/L** depending on the laboratory performing the test). If an elevated value is obtained:

- ◆ If ≥ 6.0 but ≤ 7.0 , first verify that the increase in K^+ is accurate by repeating the test **as soon as possible**. (no later than within 24 hours) This will help rule out:
 - ◆ hemolyzed sample
 - ◆ difficult blood draw requiring prolonged tourniquet placement
 - ◆ potentially offending drugs, e.g., non-steroidal anti-inflammatory medications, Septra®, K^+ sparing diuretics, K^+ containing herbal medicines, or K^+ containing salt substitutes,
- ◆ If confirmed elevated ≥ 6.0 , discontinue the RASB immediately. Complete AE.

If ≥ 7 mmol/L, this is a **medical emergency**. Send study participant to nearest Emergency Department or Urgent Care center for immediate assessment and treatment including ECG and required repeat potassium measurement ASAP (on same day). If ECG abnormality is consistent with hyperkalemia (e.g. peaked T waves, shortened QT interval, ST-segment depression) OR confirmation of potassium ≥ 7.0 mmol/L, discontinue RASB and patient should be immediately treated for hyperkalemia. Report as an SAE.

- ◆ If the elevated K^+ is not confirmed, re-institute the RASB at its usual dose and recheck K^+ again **within one week**.
- ◆ If the K^+ is confirmed to be elevated, re-institute the RASB at **half dose** and measure K^+ again one week later.

If the problem persists, discontinue the RASB permanently and notify the DCC and personal physician of this occurrence and the need for further testing to determine the cause. If the study drug is discontinued, follow the procedures outlined in paragraphs two and three of 8.9.

2. Increased serum creatinine

If serum creatinine increases by 25% or more from baseline within 3 months of introduction of RASB, or the doubling of serum creatinine over any one-year time interval, the following steps should be followed:

- ◆ Encourage the participant to maintain a well-hydrated status.
- ◆ Verify that the increase in serum creatinine is accurate by repeating the test within 2 weeks.
- ◆ If 25% or more increase from baseline is confirmed AND within 3 months of RASB introduction, reduce RASB dose by half. Complete AE. Repeat creatinine within 2 weeks. If creatinine does not improve, consider discontinuing RASB. Notify the personal physician of this occurrence and discuss the need for further testing. Report to DMC and complete AE reporting.
- ◆ If there is a doubling of serum creatinine from baseline at any one-year interval, repeat creatinine within 2 weeks. If confirmed, report to DMC. If this is an acute event, and creatinine later improves, it should be reported as an AE. If this is diabetic nephropathy progression, and there is no improvement, the subject has reached a secondary study end-point.

If the study drug is discontinued, follow the procedures outlined in paragraphs two and three of 8.9.

3. Cough

Cough can be expected to occur in approximately 10% of participants on an ACE inhibitor. The cough is usually non-productive, and is sensed as an irritating, dry feeling in the throat or pharynx. It is usually mild enough that discontinuing the medication is not necessary.

- ◆ If *mild*, encourage participant to continue the ACEI since 50% of the participants who develop cough will find it disappears in approximately 4 months.
- ◆ If a **new** persistent cough develops >4 weeks after starting the ACEI, consider another diagnosis such as post-nasal drip, asthma, or gastroesophageal reflux. Except for the post-nasal drip, the others are easily distinguishable from an ACEI cough.
- ◆ **Post-URI cough:** If the participant continues to have a cough following an upper respiratory infection, discontinuation of the ACEI for one or two weeks may result in resolution of the cough. At this point the medication should be re-introduced.
- ◆ If the cough appears to be related to the ACEI, is *intolerable* and continues for >3 weeks, reduce the ACEI dose to half. If the cough does not resolve in 2 weeks, discontinue ACEI and start candesartan (or another ARB) at equivalent dose.
- ◆ If the RASB is discontinued, follow the procedures outlined in Section 8.9.

4. Hypotension

In the rare event that this occurs, the participant should be advised to try one or more of the following:

- ◆ Maintain a well-hydrated status
- ◆ Go from lying to standing positions slowly (i.e., sitting on bed for a few minutes before standing up)
- ◆ Increase the amount of salt in their diet

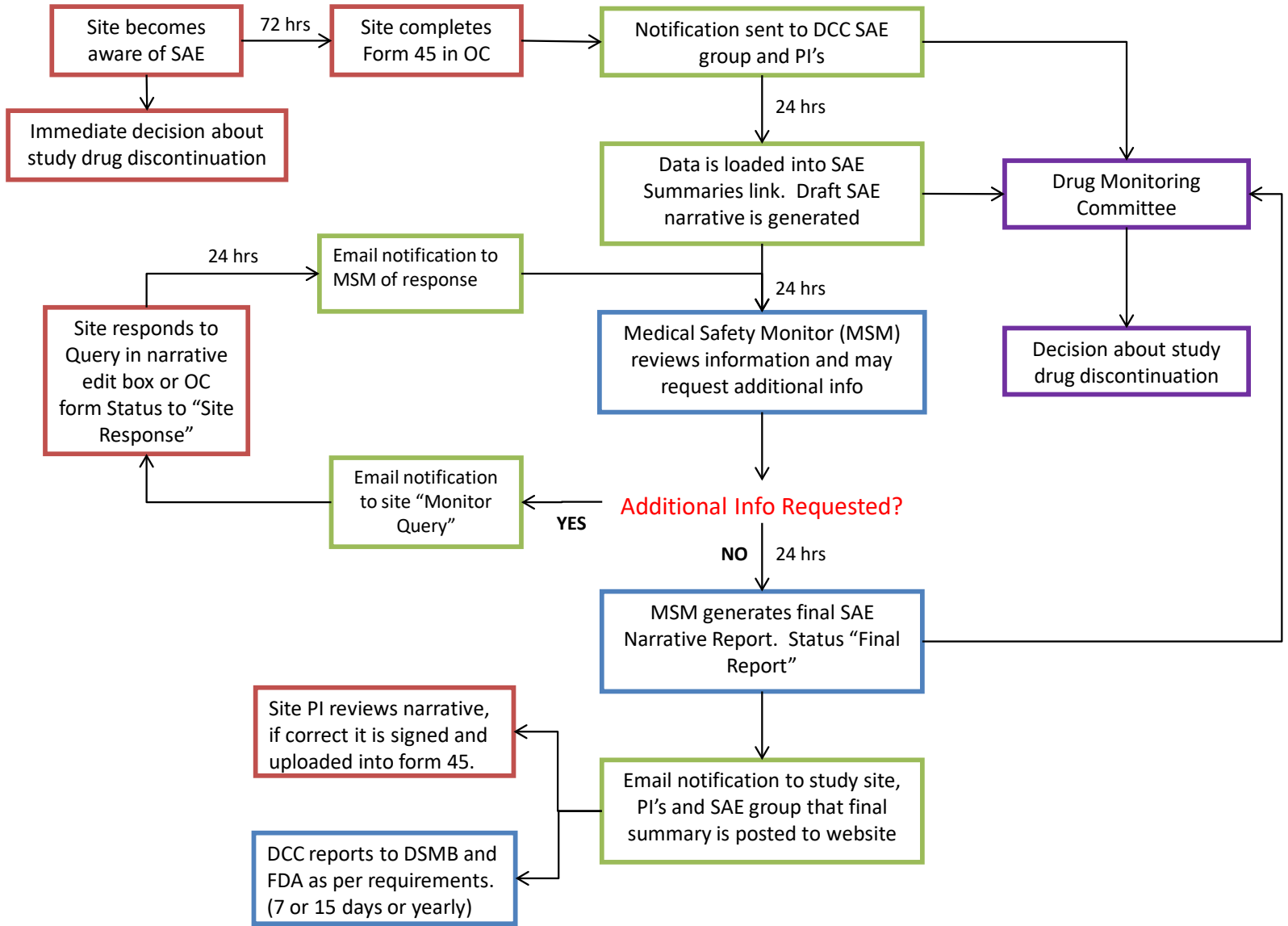
- ◆ Wear support or Teds stockings
- ◆ Take RASB and other antihypertensive medications at bedtime
- ◆ Be evaluated for other causes of hypotension as indicated, e.g. adrenal insufficiency, etc.

If hypotension persists (SBP<100 or significant lightheadedness), the dosage of non-RAS antagonist antihypertensive drugs will be progressively reduced until discontinuation, followed by a reduction of the RASB to half the dose and its discontinuation if the problem persists.

If any of the above listed events occur, AE Worksheet 20 and eCRF Form 20 should be completed, along with Worksheet 45 and eCRF Form 45 if event qualifies as an SAE. Both of these forms will capture any discontinuation in RASB or non-RASB antagonist antihypertensive drugs.

The RAS Medication, and Concomitant Medication Logs should be updated and the eCRF Forms 12 and 13 should be completed to document all changes in medication. If necessary, eCRF form 40 should be completed to document any associated protocol deviations.

8.10 SAE Process Flow Diagram



Chapter 9 PERL Study Randomization Procedure

9.0 Randomization Procedure for the Coordinator

This randomization procedure can be performed **1 day after you have completed eCRF-001R Randomization Eligibility** in OpenClinica. This will give you the randomization number that will be provided to the pharmacist in order for them to get the treatment group assignment.

- To be eligible for randomization, the participant:
 - Must have SBP≤150 or DBP≤95mmHg
 - Must have a valid baseline (V4) iGFR measurement (confirmation of your valid iGFR will be sent to you by email from the DCC PERL PM)-DO NOT randomize any subject prior to receipt of this confirmation).
 - DNA testing indicates that the HLA B*58:01 allele is absent/negative

- Stratification factors are:

Central Lab Visit 1 value for HbA1c and Central Lab Visit 4 value for uric acid

It may be helpful to highlight the stratification factors on the Central Lab faxed results and have them available at the time of randomization.

- Randomization Process
 1. Go to PERL main site at: <http://perl-study.org/>
 2. Click on PERL Intranet
 3. Login with your personal login ID and enter your assigned password and click on Login button
 4. Click on "**Rando**" link
 5. The randomization page will open:



Subject ID:

Central Lab Visit 1 HbA1c: **- Blank** ▲
≤ 7.8% ■
> 7.8% ▼

Central Lab Visit 4 Serum Uric Acid: **- Blank** ▲
≤ 6 mg/dL ■
> 6 mg/dL ▼

Get_Randomization #

Enter the **Subject ID**, **Central Lab Visit 1 HbA1c**, and **Central Lab Visit 4 Serum Uric Acid** above, then click on the Get Randomization # button

6. You will see the randomization confirmation page:

RESULTS:	
Subject ID:	02AP7294
Randomization ID:	122009
Randomized By:	Donna E DiFranco (donnadi)
Randomization Date:	Monday , April 21, 2014, 10:08:38 AM
HbA1c:	≤ 7.8%
Serum Uric Acid:	> 6 mg/dL
QUERIED BY:	
USER:	Donna E DiFranco (donnadi)
ROLE:	Coordinator (Test)
SITE ACCESS:	Steno Diabetes Center
DATE:	Tuesday , April 22, 2014, 11:53:01 AM

Please print this page for your study binder using the Print button shown below.

Print

7. Confirm that the correct ID and stratification factors have been entered.
8. If there is an entry error, PRIOR to printing, the factors can be changed.
9. If you forget to print the page, you can repeat steps 3-8 to view the randomization screen again.
10. If you notice an entry error, AFTER printing, contact perlstudy-pm@umich.edu

9.1 Electronic Unblinding Instructions (Refer to 7.6.1 of the MOO, “Breaking the Blind” for more information regarding appropriate use of this option)

➤ Unblinding Process

1. Go to the PERL Study’s main website at: <http://perl-study.org/>
2. Click on PERL Intranet
3. Login with your personal login ID and enter your assigned password and click on the Login button
4. Click on Randomization button
5. Select “break blind”
6. Enter ID Number – select YES
7. Treatment group is provided
8. Complete eCRF #41 (Unmasking) in OpenClinica
9. Print form for your records

Chapter 10

Informed Consent

10.0 Informed Consent Documents

The PERL Executive Committee has provided three protocol-specific informed consent templates to the Data Coordinating Center (DCC), which are posted on the PERL website. Each PERL study site will customize the templates and receive approval from their study site's human subject protection committee (IRB/REB) prior to its use.

Each site can determine which ICF to use, depending on whether the participant will be seen on site or remotely. A description of each ICF is provided below:

Screening ICF: This ICF is **ONLY** for **Screening visit (V1)**. This template was developed primarily for use when the patient chooses to only determine initial eligibility to the study, based on medical history, BP measurements, and blood/urine testing. As approximately 50% of those patients screened are deemed ineligible, this simplified version allows the patient time to think about whether they wish to commit to the full study, if eligible. If eligibility is confirmed at Visit 1, the patient will then need to sign a second ICF for participating in the remaining study visits. This ICF is called the Post-Screening Treatment Phase ICF.

Post Screening Treatment Phase ICF: This ICF is for V2-V17. Patients who have only signed the Screening ICF, and are deemed eligible, will be **required** to complete the Post-Screening Treatment Phase ICF. This ICF goes into detail about what the patient can expect in the remainder of the study visits (V2-V17).

All Inclusive ICF: This ICF includes *both* the Screening *and* Post-screening visits (V1-V17) details, combined in one ICF. This will be used if the patient chooses to commit to the study at the initial visit and will be coming to your site for most/all visits; or only for the iGFR procedures.

Each site can determine, based on their circumstances, which ICF would be most suitable.

The written informed consent should be brief and written in plain language so that a participant with an eighth grade education level can understand the contents. The participant should sign and date the informed consent form, and should also receive a copy of the signed and dated informed consent form. The study site must maintain a signed, original copy of the informed consent document for each consented subject, in the subject's study binder.

Good Clinical Practice (GCP) guidelines require that source documents should indicate that the study was explained and the participant had time to ask questions before the informed consent form was signed. No collection of data related to the study or procedures will be done prior to completion of the informed consenting process. This can be a stand-alone document, or it can be included in a progress note in the subject's binder.

The informed consent will include the following required Basic and Additional Elements:

Checklist of Federally Required Elements of Informed Consent - 21 CFR 50.25	
	A statement that the study involves research
	An explanation of the purposes of the research
	The expected duration of the subject's participation
	A description of the procedures to be followed
	Identification of any procedures which are experimental
	A description of any reasonably foreseeable risks or discomforts to the subject
	A description of any benefits to the subject or to others which may reasonably be expected from the research
	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For studies under FDA oversight it must also note the possibility that the Food and Drug Administration may inspect the records.
	For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
	An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
	A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled
Additional elements, as appropriate	
	Location of study posting on the internet: ClinicalTrials.gov
	Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
	Any additional costs to the subject that may result from participation in the research
	The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject

	A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
	The approximate number of subjects involved in the study

10.1 Obtaining Informed Consent

For the PERL study, written informed consent **must** be obtained on or *prior to* Visit 1 and before any study procedures are performed. If V1 is conducted remotely (i.e., the study visit is conducted over the phone and biospecimens are collected at a local lab), the ICF should be sent to the participant by email, mail, or fax and a signed copy returned to the study site *before* any study procedures are performed.

The Study Physician and/or Clinical Research Coordinator (CRC) will discuss the study and the informed consent in detail with the participant **prior** to obtaining consent.

Since this study falls under the FDA's oversight, the consent must be dated when signed by the participant. The consent should be signed and dated by the investigator or designee (designee must be documented on the Delegation of Authority log). A copy of the ICF should be given to the participant, as well as a copy maintained in the patient's research binder. Documentation that the ICF was discussed, explained, and reviewed; all questions/concerns were answered; the participant had ample time to review the ICF and discuss participation with family members/others; and the participant signed/dated the ICF should be documented in the patient's research binder. A template entitled "*Documentation of Informed Consent Process for Onsite Subject File*" is located at the end of this chapter for site use; a document may also be developed at each site for this purpose.

If your institution requires that a copy of the signed informed consent be filed in the participant's medical record, documentation that this has occurred is required. Institutional guidelines may also require a copy of the ICF be sent to your IRB. Please check with your institution.

Failure to give informed consent renders the participant ineligible for the study. **NO** research testing /procedures may occur nor may any study medication be given before obtaining informed consent.

10.2 Re-consent

If there is a change in any of the study procedures that may affect the participant's safety or willingness to participate, the informed consent document must be revised and again approved by the Institutional Review Board (IRB). Any participants enrolled in the study prior to such changes may be required to sign an amended consent form, depending on local IRB requirements.

NOTE: Participants, who have enrolled in the PERL study under the PERL Version 6.0 or Version 7.0 protocol, will need to be re-consented under Version 8.0. A copy of all signed ICF's should be maintained in the patient's binder.

10.3 Health Insurance Portability & Accountability Act (HIPAA) Compliance

At most study sites, a HIPAA form is presented to a potential participant for signature, in addition to the informed consent form, unless the necessary assurances are incorporated into the informed consent form. The HIPAA form describes subject and data confidentiality associated with the study. This form is not necessary at non-US sites. At these locations, it may be substituted by a corresponding form addressing local confidentiality requirements.

10.4 Non-English-Speaking Participants

Many IRB's mandate whether a translated consent document is needed to obtain consent from non-English speaking participants or whether a translator can be used to obtain consent. Each study site must conform to their local requirements.

10.4.1. Other issues related to translators

- A Human Protection certificate is not needed for the translator because the translator is only translating what the health care professional is stating; they do not provide patient care or collect data.
- Translation of any instructions is the responsibility of the study site and should be handled in the same manner as for non-research participants.
- All expenses and budget issues related to using translators are study site-specific and should be discussed with the site Director.

NOTE: Translator issues are study-site specific; they are the responsibility of the study site /site Director.

Visit 17 Completion Timeline

Site should make all possible attempts to schedule participant's visit as per protocol. In circumstances when a site determines that a subject is not coming for protocol-scheduled visits for more than 8 months; efforts should be made to schedule participant's last visit in the study. Timelines to perform last iGFR in the study is as follows:

- 2 months +/- 2 weeks from target V17- is the window. Beyond + 2 weeks record a protocol deviation.
- Max 4 months from target V17- Beyond 4 months from V17 or beyond June 15, 2019 participant is not eligible for a final iGFR unless approved by the study PIs

It is important to contact study PIs and DCC if there is any deviation in the above criteria.

If the site is certain that a subject will not return to the study, please follow the guidance on inactive subjects as mentioned in MOO.

Subjects pending visits > 8 months since last visit

Last study visit and iGFR procedure can be performed by 3 years and 4 months (max) after randomization. DCC and study PIs should be informed if site is waiting for participant's visit for more than 8 months via email. Beyond June 15, 2019 participant is not eligible for a final iGFR unless approved by the study PIs.

Data entry openclinica should be completed on real time basis in these cases especially final status form, ESRD and log pages.