

MANUAL OF PROCEDURES (MOP)

QUARTET USA:

A double blind randomized controlled trial to assess the efficacy and safety of a quadruple ultra-low-dose treatment for hypertension

April 6, 2021

Version 8.0

IRB Number: STU00205834

List of Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE-I	Angiotensin-converting-enzyme inhibitor
AE	Adverse event
ALP	Alkaline phosphatase, a liver function test
ALT	Alanine transaminase, a liver function test
API	Application Programming Interface
ARB	Angiotensin II receptor blocker
AST	Aspartate Aminotransferase, a liver function test
BB	Beta blocker
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft, a type of surgery that improves blood flow to the heart
CAD	Coronary artery disease
CCB	Calcium channel blocker
CRF	Case report form
DBP	Diastolic blood pressure
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
ECG/EKG	Electrocardiogram
eConsent	Electronic consent
ECT	Electroconvulsive therapy, a medical treatment used in patients with severe, major depression
eGFR	Estimated glomerular filtration rate, which estimates kidney function
HER	Electronic health record
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase, a liver function test
HDL-c	High density lipoprotein cholesterol
IPD	Individual participant data
LVH	Left ventricular hypertrophy, or muscle thickening of the heart's left pumping chamber
MI	Myocardial infarction, also known as a heart attack
MOP	Manual of Operating Procedures
PCI	Percutaneous coronary intervention, a non-surgical procedure to open narrowings or blockages of the coronary arteries
PROMIS	Patient-Reported Outcome Measurement Information System
QRS	An ECG-derived interval that represents ventricular depolarization
QTc	An ECG-derived interval that represents the time from ventricular depolarization to repolarization
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SBP	Systolic blood pressure
TIA	Transit ischemic attack, a stroke-like attack resolves within 24 hours
UACR	Urine albumin: creatinine ratio

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QUARTET USA:

A double blind, randomized controlled trial to assess the efficacy and safety of a quadruple ultra-low-dose treatment for hypertension

Co-Principal Investigator: Mark D. Huffman, MD, MPH

Co-Principal Investigator: Jody D. Ciolino, PhD

1. INTRODUCTION AND OVERVIEW

The purpose of this document is to outline operating procedures for the QUARTET USA clinical trial. The QUARTET USA trial is a two-armed, double-blind, randomized controlled trial with the aim of assessing efficacy and safety of a quadruple ultra-low-dose treatment for hypertension when compared to standard monotherapy. The trial is sponsored by the NIH / NHLBI through grant award #R61HL139852; Co-Principal Investigators: Mark D. Huffman, MD, MPH and Jody D. Ciolino, PhD. The principal investigators and coordinating activities for the trial are located at the Northwestern University in the Department of Preventive Medicine, Feinberg School of Medicine in Chicago, IL. The trial activities will occur at selected site(s) that are a part of Access Community Health Network (ACCESS), a network of 36 federally-qualified health centers (FQHCs) in the Chicagoland area. The trial Operations Team, comprised of leadership at Northwestern University, ACCESS Center for Discovery and Learning, and University of Sydney (Australia) oversees the general scientific direction of the trial, guiding the conduct and implementation.

The procedures contained within this document are a guide and complement the Study Protocol. The manual of operating procedures (MOP) is the principal supporting document to the study protocol that all study staff must follow to ensure proper compliance with standardized procedures and regulations set forth by federal, state and institutional boards and committees. This document may be updated as the study progresses and is subject to version control.

If you have any questions that are outside the scope of this document or require that an update to this document be made, please contact one of the following individuals:

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Hiba Abbas

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2. ROLES AND RESPONSIBILITIES

Management and Communications

Details of the trial related management and communications are found in the QUARTET USA Management and Communications Procedure.

Study Organizational Structure

Details of the organizational structure are found in the QUARTET USA Management and Communications Procedure.

Core Study Team Members

Team Member	Affiliation/Role	E-mail Address	Location
Mark Huffman	Principal Investigator	mark.huffman@nm.org	Northwestern University
Jody Ciolino	Principal Investigator	jody.ciolino@northwestern.edu	Northwestern University
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Edgar Pizarro	Sr. Research Study Coordinator	edgar.pizarro@achn.net	Access Community Health Network
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Fallon Flowers	Research Nurse	Fallon.flowers@achn.net	Access Community Health Network
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Tyler Jacobson	Intern	tyler.jacobson@northwestern.edu	Northwestern University
Adriana Quintana	Research Assistant	adriana.quintana@achn.net	Access Community Health Network
Alexandra Soriano	Research Assistant	alexandra.soriano@northwestern.edu	Northwestern University
Aashima Chopra	Statistical Analyst	aashima.chopra@northwestern.edu	Northwestern University

June 15, 2020 personnel updates:

- Edgar Pizarro's role has been replaced by Fallon Flowers
- Mianzhao (Tracy) Guo has stopped working with the study team
- Tyler Jacobson has begun working with the study team

September 21, 2020 personnel updates:

- Alexandra Soriano has begun working with the study team

- Adriana Quintana has begun working with the study team
October 23, 2020 personnel updates:
- Aashima Chopra has begun working with the study team
March 1, 2021
- Priya Tripathi has begun working with the study team

Training Plan

All individuals involved in the conduct of human subjects' research must complete human subjects' protection training and recertify every three years. Training is satisfied by completion of the CITI Basic Biomedical Course and accompanying Refresher course every three years. In addition, all individuals involved in the conduct of clinical trials must complete the Good Clinical Practice (GCP) training; there are multiple options for completing this component according to Northwestern University's IRB (i.e., CITI Training Module on GCP; <https://www.nucats.northwestern.edu/education-and-career-development/good-clinical-practice-training/index.html>).

All study team members involved in execution of any portion of the procedures outlined in governing QUARTET USA documents, including the Manual of Procedures, Protocol, ICF and supporting documents, must certify review and understanding of the applicable documents through signature in the trial training log. The training log is an active document.

3. STUDY OVERVIEW

Enrollment Timeline

The clinical trial will recruit 364 participants between the beginning of Year 2 through the beginning of Year 4 of the grant life. Year 5 will serve to finish any remaining follow-up visits and analysis of collected data. Initial participant enrollment is projected for Q1 of Year 2, but it will be contingent on regulatory approval. We anticipate enrollment will conclude in Q1 of Year 4 of the study grant.

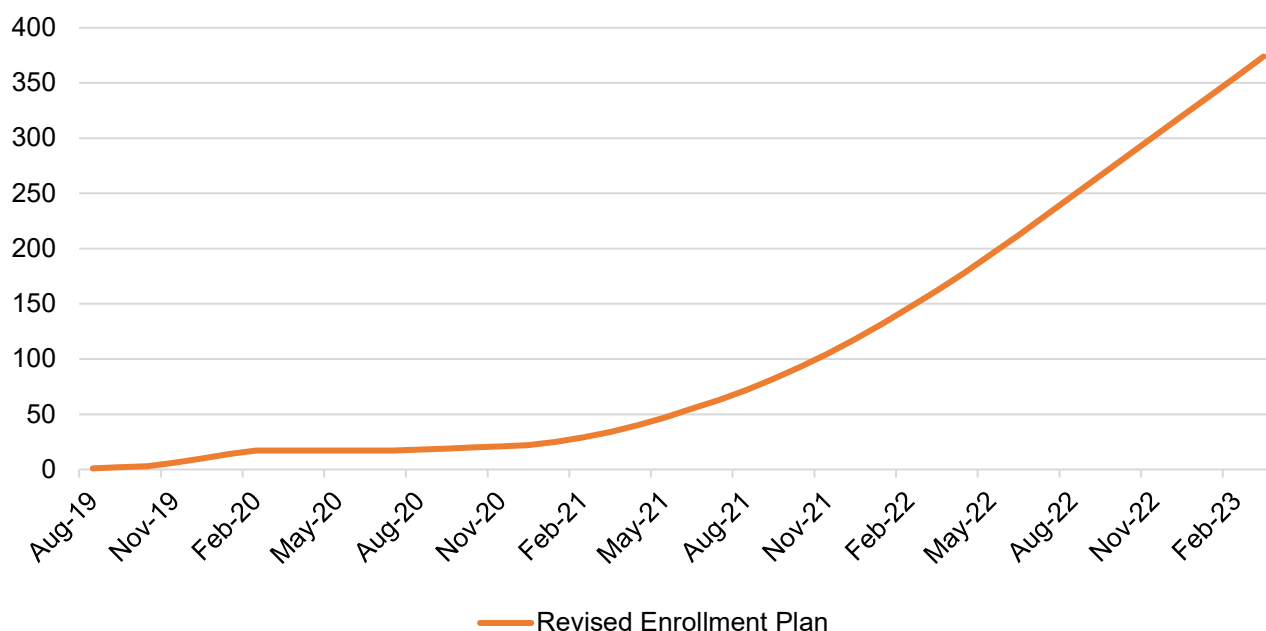
Study Recruitment Sites

Participant recruitment will take place solely through the ACCESS Community Health Network (ACHN). ACCESS has a diverse patient population, served throughout the Cook County and DuPage County areas. Recruitment will be initiated at the ACCESS Martin T. Russo Family Health Center located at 245 S Gary Avenue, Bloomindale, IL 60108. The second recruitment site will be the Ashland Family Health Center located at 5159 S Ashland Ave, Chicago, IL 60609.

Recruitment Targets

Enrollment was initiated in August, 2019. By March 2020, 17 patients were enrolled and randomized. Between March 2020 and July 2020, no participants were recruited due to cessation of non-essential activities at the clinical sites during the COVID-19 initial pandemic. Recruitment was restarted in late August 2020 and the overall study timeline was extended into Summer of 2022. During Years 2 through 4, steady state enrollment will comprise 16-17 patients per month. All recruitment rates will be closely monitored during the duration of the study. Once the recruitment target has been achieved, further recruitment will be stopped.

Figure 1. Revised enrollment plan as of January 2021



Site Performance Plan

Prior to initiation of study procedures at a clinical site, the site leadership (office manager, clinical staff, etc.) will meet with the QUARTET USA Operations Team to ensure understanding and agreement of trial procedures. The QUARTET USA Operations Team will pilot test the study protocol and procedures as outlined in this MOP and other supporting documents prior to the first participant's randomization. Additionally, the Data Safety and Monitoring Plan (DSMP) outlines on-site monitoring visits by a contracted third party for initiation, targeted on-site monitoring, and for closeout procedures.

Once the study initiates at the site, recruitment will be monitored through Research Electronic Data Capture (REDCap) reports and through Data Status and Quality Reports (DSQRs) as indicated in the Data Management Plan (DMP) at minimum every two weeks. These reports will also summarize general protocol adherence and performance of the site through screening failure rates, drug accountability, adverse events, and other essential data as mentioned in the DMP. The central monitoring approaches in place are meant to identify issues both at the participant level and at the site level that may warrant any corrective or preventative action(s). The study coordinator and research nurse will also provide regular updates about recruitment to the operations team.

If a site is underperforming, recruitment is lagging, or at the general discretion of the Executive Director of Research, Danielle Lazar and Jairo Mejia, MD, Chief Medical Officer, additional recruitment site(s) may be selected. As sites are added, the study team will ensure IRB approval prior to initiation of enrollment at those sites and continuation of the central monitoring approaches along with the general approaches as mentioned in the DSMP.

Study Endpoints

Primary, secondary, and exploratory endpoints are listed within the Study Protocol.

Study Inclusion/Exclusion Criteria

Study inclusion and exclusion criteria are listed within the Study Protocol.

4. DETAILED STUDY PROCEDURES

Study Flow

Figure 2 contains study time points and procedures required for participation in QUARTET USA. QUARTET USA will enroll 364 patients in 1:1 ratio into the LDQT (experimental) arm and the candesartan-only (active control) arm. Participants will complete a six-week follow-up visit to assess their medication adherence, record any potential adverse events associated with the medication and assess blood pressure control through office blood pressure.

Participants will then be asked to return after another six weeks have passed (12-weeks post-baseline / randomization visit) to assess medication adherence, return any medication not taken, record any potential adverse events, and assess blood pressure through office blood pressure.

Figure 2. Study Schematic

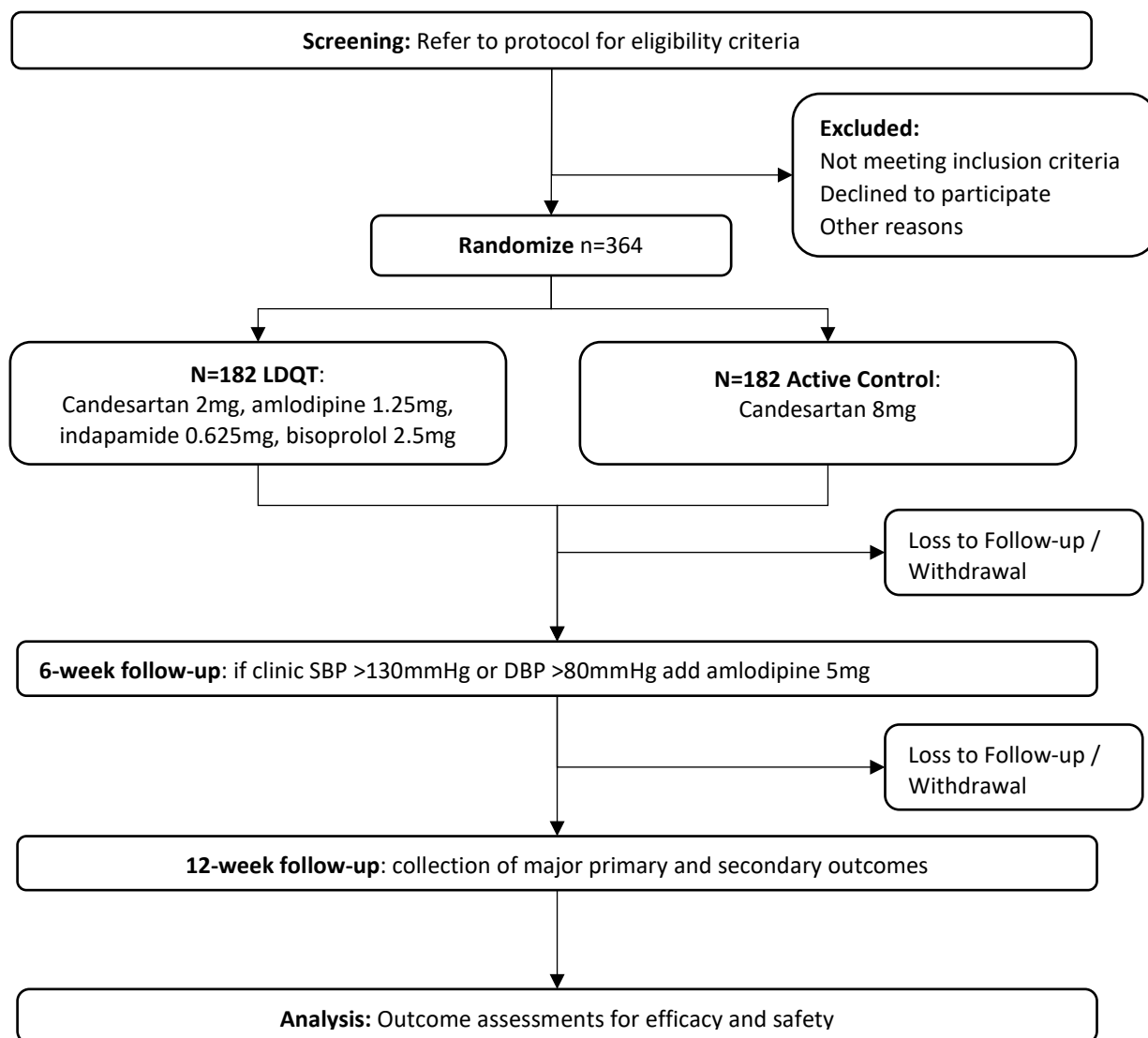


Table 1: Visit Activities and Roles

Study Timeline	Screening and Randomization		6-Week Follow-up Visit	12-Week Follow-up Visit		Anytime
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Chart Review
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Chart Review
Location	Clinic with telehealth screening and eConsent option	Clinic	Clinic	Clinic	Clinic	
Study Activities						
Screen Flag for Review						SP
Informed consent ¹	SC/RN					
Demographics ¹	S					
Automated office (clinic) blood pressure measured in the previous 12 weeks ^{1*}	SP					
Blood pressure and heart rate measurements, by research team	SC/RN		SC/RN	SC/RN		
ECG	SC/RN					
Interpret ECG	SP					
Anthropometrics and Medical history ¹	SC/RN					
Concomitant medications ¹	SC/RN S		SC/RN S	SC/RN S		
Lifestyle questions ¹	S					
PROMIS global health ¹	S			S		
Laboratory assessments	L		L	L		
Out of Range Lab Review						SP
24-hour ABPM (Optional)	SC/RN S			SC/RN S		
24-hour ABPM Return		SC/RN S			SC/RN S	
Inclusion and exclusion criteria	SC/RN					
Randomization		SC/RN				
Study Drug dispense		SC/RN	SC/RN			
Study Drug return			S	S		
Medication adherence			SC/RN S	SC/RN S		
Participant status	SC/RN	SC/RN	SC/RN	SC/RN	SC/RN	SC/RN
Health service utilization	S		S	S		
AEs and SAEs	SC/RN S	SC/RN S	SC/RN S	SC/RN S	SC/RN S	SC/RN S
Beliefs about medications	S			S		
TSQM			S	S		
NVS	RN S					

L	Clinic Lab
RN	Research Nurse
S	Self-Report (Participant)
SC/RN	Study Coordinator and Research Nurse

SP	Study Provider
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¹This form may be completed electronically via a telehealth visit up to 90 days before the date of randomization (12 weeks in the case of previous automated office blood pressure).

*The clinic blood pressure will be observed by a healthcare professional within the clinic, but the SC/RN may review and abstract these data from the EHR to assess eligibility.

PROMIS: Patient Reported Health Outcome Measurement Information System; ABPM: Automatic blood pressure monitor; AE: Adverse event; ECG: Electrocardiogram; SAE: Serious adverse event; TSQM: Treatment Satisfaction Questionnaire for Medication

Screening and Recruitment

Participants will be initially recruited from one of the of the health centers within Access Community Health Network through Epic. Additional health center sites will be used through Access Community Health Network if there is a lag in recruitment or if there are issues as indicated in the Section: Site Performance Plan above.

Potential participants will be sent informational brochures about the study through the mail and will be given the study coordinator's contact information if they are interested in participating. We plan to use a multifaceted screening / recruitment strategy:

1. A query developed with the information systems (IS) team at ACCESS that will allow rapid electronic identification of potentially eligible participants based on clinical data documented in the medical record. The query is based on inclusion / exclusion criteria from the study protocol.
2. Provider referral: providers at the health center will be able to refer patients that they deem would benefit / be potentially eligible to participate in the study. The referred patients from the providers will be screened through Epic before contact is made.
3. Self-referral: participants receiving study material either through advertisements / recruitment materials or mailed brochures will contact the study coordinator if they are interested in participating. These participants who self-refer will also be screened in Epic before scheduling the eligibility visit.

Patients who are potentially eligible as identified by the IS query will be housed within the research portal within the Epic system. The Northwestern University team have compiled a separate **SCREENING: QUARTET USA** REDCap database to house data related to potential study participants. These data will not be downloaded nor summarized by study team members other than those conducting screening and consenting activities (i.e., those indicated as potential data enterers), and they will be used to generate potential lists / reports of participants for those conducting consenting and screening visits.

The research coordinator / study nurse will contact participants who meet the eligibility criteria from the Epic screening to provide them with information about the study. Initial screening and consent may take place through telehealth visit that uses a 21 CFR, Part 11 instance of REDCap, or through an in-person screening visit. The Northwestern University team have compiled a separate **eConsent: QUARTET USA** REDCap database to house data related to potential study participants who would prefer consenting electronically using the 21 CFR, Part 11 compliant eConsent workflow. These data will not be downloaded nor summarized by study team members other than those conducting screening and consenting activities (i.e., those indicated as potential data enterers).

Screening and Eligibility Visit

Individuals who are interested in the study and initially meet eligibility criteria should be scheduled for a visit at the health center with the research nurse or through telehealth with the research nurse or research coordinator as soon as it is convenient. Information from the first visit will be gathered in the CRFs. Any participants signing consent, whether randomized thereafter, will have a record in the study database. The information collected on the screening / baseline forms will further determine if the participant is eligible based on the criteria listed in Inclusion and Exclusion Criteria CRF.

If a telehealth visit is conducted prior to randomization, then all information collected during these visits will be documented electronically using a 21 CFR, Part 11 compliant instance of REDCap. During in-person screening or randomization visits, any electronic information will be verified and documented on paper CRFs. If data collected from a telehealth visit were through an electronic survey completed by the participant, then a printed survey with completed response will serve as the paper CRF version. Any updates to previously reported information will be made at that point in time both electronically and if necessary, on paper versions of CRFs in accordance with Good Clinical Practice guidelines (i.e., single line through any updates with initials and dates).

If required laboratory assessments have not been completed within the past three months, they must be completed during the screening visit to ensure eligibility. An ECG will also be completed by the research nurse and interpreted by the study provider. Both the ECG and laboratory results will help further determine if the participant is eligible to enroll into the study.

Enrollment Procedures

- Only patients who provide written or electronic informed consent can proceed with the screening and baseline assessments to determine eligibility.
- If the patient does not proceed to enrollment, then the research coordinator / study nurse / investigator will update the research portal and indicate the reason(s) for ineligibility.
- After providing informed consent, the participant will complete: demographics, blood pressure and heart rate measurements, ECG or AliveCor KardiaMobile Personal ECKG, medical history, lifestyle questionnaire, global health assessment, laboratory assessments (if applicable, as above), and the optional ABPM assessment. These data will collectively help determine eligibility for each participant.

Participant Study Identification Number: Record ID

Participant data entry will be performed at the chosen health center(s) through both paper CRFs and eCRFs (REDCap). Access to REDCap is restricted to those with affiliate “NetIDs” and passwords.

All participants will receive a study identification number that will serve as their principal identification throughout the enrollment of the QUARTET USA study. The number will be used for reference during the study and will be added to all study documents. Any communication regarding the participant will refer to him / her by this Record ID. In the database, this field will be labeled “Record ID” and coded: “subid”. The first participant **at the Russo site** will be given **Record ID: 1001, the second will be 1002, the third will be 1003, and so on.** The first participant **at the Ashland site** will be given **Record ID: 3001, the second will be 3002, the third will be 3003, and so on.** The research nurse and study coordinator will take care to **consult the electronic database to determine the next record ID in the sequence.**

All consented participants will be assigned a Record ID; if a participant is subsequently deemed ineligible, he / she will be indicated as such in the study database on the Participant Status CRF, and Manual of Procedures: April 6, 2021

his / her record will be completed. Thus, it is possible that participants receive a Record ID, but do not officially enroll in the study (i.e., they are not randomized).

To assign a participant a new Record ID within REDCap, study staff will:

1. Log into REDCap with their NetIDs and passwords.
2. Locate and select the REDCap project corresponding to the site:
 - a. **“QUARTET USA”** corresponds to the Russo site (initial study site).
 - b. **“QUARTET USA – Ashland”** corresponds the Ashland site (second study site).
3. Select “Add / Edit Records” on the left panel within the QUARTET USA project.
4. Select Arm 1: Main Assessments.
5. Type the next **four-digit record ID** within the sequence in the “Enter a new or existing Record ID”. Note: to view those IDs already assigned, either use the REDCap report feature in the application panel or view the dropdown of existing Record IDs.
6. After typing in the new Record ID, click anywhere on the screen to be taken to the new participant’s blank record. **Data must be entered and saved in at least one field for this record to be documented within the REDCap database.**
7. **After** initial data entry into the Main Assessments REDCap arm for a participant, enter a new record with **the same Record ID** into **Arm 2: AE**.
 - a. This is imperative for logging and tracking any AEs for a participant should they occur.
 - b. There should be a message similar to the following: **“NOTICE: Please note that Record ID “XXXX” also exists on another arm”. This is an added check to ensure that the participant with the new Record ID has a record in EACH arm within REDCap.**
 - c. To initiate / save data for the new Record ID in the AE arm, navigate to the **AE Tracking** form, mark it as “Complete” and save / exit the form. This is a placeholder or “dummy” form that contains a read-only, default SAE admin email address to ensure any documented SAEs will trigger an alert to those included in the QUARTET USA Safety Listserv.

Participant File

The research coordinator and study nurse will compile a Participant File for each participant that is enrolled in the study. The files will hold the following documents:

- Participant identification enrollment log
 - Includes specific participant information including name, date of birth, study identification numbers, and medical reference number
- Informed consent
 - Signed by both the participant and study personnel enrolling the participant (research coordinator/study nurse)
- Paper CRFs
 - The forms should be dated and signed by the study personnel recording the data before being transcribed to REDCap
- All supporting medical documents
 - ECG copies
 - Laboratory results (if printed)
 - ABPM diaries
- Any related file notes

The nurse and coordinator will also maintain a separate set of files for participants that are not enrolled (i.e., deemed “screen failures”) in the study but have consented and completed some assessments documented in the CRFs during the screening process. All participant files will be kept in a locked file cabinet which, in turn, will be locked in a closet. All electronic study data will be housed on Northwestern University’s REDCap platform, and potentially stored in secure “FSMResFiles” drives located on Northwestern University’s Feinberg School of Medicine’s servers.

Informed Consent and HIPAA

At the in-person screening or through a telehealth visit, prior to any baseline or screening assessments, the informed consent form will be reviewed with each participant along with a witness (research coordinator or the study nurse).

- If conducted in person, then both the participant and witness will sign and date two copies of the consent form if the participant agrees to the study procedures. A hard copy will be kept in the participant’s file, housed at the health center where the study is being conducted (in a locked file cabinet in a locked closet). The participant will be provided with the other copy to take home.
- If conducted via a telehealth visit, then the participant will have two options on how to complete the consent:
 - Option A: eConsent Framework. The participant will receive the consent form as an automated survey sent from the eConsent: QUARTET USA REDCap database. This database will house all eConsents (across all sites) for those wishing to use this option. The participant will electronically sign and date the consent form, which will be stored in REDCap. The witness (i.e., person obtaining consent) will electronically sign and date the consent form after the participant has completed the REDCap eConsent survey. A final person verifying all documents within the eConsent record will compile, sign, and date documentation for this verification. All documents eConsent surveys have been enabled under the eConsent framework within REDCap and will be stored in the “vault,” which is 21 CFR part 11 compliant as of January 2021. Access to all surveys is restricted to only those individuals involved in the eConsent process through a “shared secret” field. This value is entered in the “Record Creation & Consent Routing” form within the eConsent REDCap database. A hard copy will be kept in the participant’s file, housed at the health center where the study is being conducted (in a locked file cabinet in a locked closet). The participant will be sent a pdf of the executed electronic consent form via email.
 - B. The participant will receive a hard copy of the consent form in the mail or will print out a copy that is emailed to them. The participant will provide a wet signature and date the consent form and will upload and image of the last page with their signature to their ACCESS MyChart account. A copy of the consent signature page will be saved in their Epic chart under the media manager tab. The witness will be able to print the signed form and provide a wet signature and date. A hard copy will be kept in the participants file, housed at the health center where the study is being conducted (in a locked file cabinet in a locked closet).

The HIPAA authorization form will be combined with the informed consent and will be located on the bottom of the form.

5. STUDY ASSESSMENTS

The following is a list of CRFs / study assessments, and a brief description of each. It should be noted that the names of the paper CRFs and the eCRFs differ slightly. The REDCap names for the eCRFs are condensed in comparison to the paper forms for data management purposes. The mapping of the two different sets of forms is indicated in the table below.

Paper CRF Names	REDCap eCRF Names
Informed Consent	Informed Consent or refer to eConsent: QUARTET USA database
Demographics	Demographics
Newest Vital Sign	NVS
Blood Pressure and Heart Rate	BP and HR
ECG*	ECG, ECG Review
Anthropometrics and Medical History*	Medical Hx
Lifestyle Questions	Lifestyle
Laboratory Assessments*	Labs
24-hour ABPM*	ABPM
Inclusion and Exclusion Criteria	Eligibility
Randomization	Randomization
PROMIS Global Health	Global Health
Belief About Medicine	Belief
TSQM	TSQM
Medication Adherence	Adherence
Health Service Utilization	Health Service
Concomitant Medications Form	ConMeds
Participant Status	Participant Status
Protocol Violation	Protocol Violation
Drug Tracking	Drug Tracking
Form Tracking – Not applicable for paper CRFs	Form Tracking
Adverse Events Form	Adverse Events, AE Tracking, SAE Review

*Indicates “source” documentation may come from medical record for components of these assessments or from an external file (e.g., ABPM).

A brief explanation of each form is included below:

Demographics (participant facing)

This questionnaire will be completed at the baseline visit and will assess the participants’ social and economic status, ethnic group, and country of birth.

Newest Vital Sign

The Newest Vital Sign is an assessment tool that will be utilized to determine the participants’ health literacy level. It will be assessed at baseline for all study participants, but does not need to be completed prior to randomization.

Blood Pressure and Heart Rate

This form includes the documented automated clinic blood pressure (used to assess eligibility) and both observed blood pressure and heart rate by research staff and research grade blood pressure and heart rate measures.

ECG or AliveCor KardiaMobile Personal EKG

This form will be completed by the study provider reading the ECG or AliveCor KardiaMobile Personal EKG. The research nurse or study coordinator will perform the ECG or AliveCor recording, and results will be sent to the clinical provider for interpretation and completion of this form. Refer to the detailed procedures below.

Anthropometrics and Medical History (partially participant facing)

This form will document weight and height at baseline, the participants' hypertension history, and other medical history. This form will be completed at baseline, during screening, and it will help determine eligibility.

Lifestyle Questions (participant facing)

The questionnaire will be completed at the baseline visit and will assess the participants' consumption of alcohol, smoking, and diet / exercise habits.

Laboratory Assessments

This form contains information from urinalysis, blood test, and lipid panel results. Laboratory assessments will be completed at baseline (or within three months prior), Week 6, and Week 12 visits.

24-hour ABPM

This form will include both an upload of the automatically-generated output from the ABPM machine for the given participant at the study-specific time point and the relevant summary values for blood pressure and heart rate to allow for safety / eligibility assessments.

Inclusion and Exclusion Criteria

This form includes a list of all inclusion and exclusion criteria as defined in the study protocol. As appropriate, information from preceding forms that will help determine eligibility is "piped" into the electronic version along with calculated fields to check eligibility according to the data entered electronically. This will help in ensuring participants meet eligibility requirements prior to randomization.

Randomization

This form contains the date of randomization, an indicator that the participant meets requirements for randomization, and the study drug kit number to which each participant is assigned. In order for participants to be randomized, the study staff must select "randomize" within REDCap to obtain the kit number.

PROMIS Global Health (participant facing)

Quality of Life (QOL) will be assessed at baseline through the PROMIS Global Health tool, which contains 10 questions. The questionnaire will be completed independently by the participant at baseline and at the 12-week follow-up visit.

This tool asks some questions pertaining the mental health relating to their overall mood, depression, anxiety, and irritability. In the rare occasion that the participant discloses information about having suicidal ideations, or a new onset of a mental health condition alert the participants provider or clinician at the health center immediately.

Beliefs about Medicine (participant facing)

The Beliefs about Medicine Questionnaire (BMQ) will be assessed at baseline and Week 12 for all study participants as part of the implementation aims of the study. At baseline, this instrument does not need to be completed prior to randomization

TSQM (participant facing)

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a validated scale used to assess participants' satisfaction with their medication at Week 6 and Week 12. This questionnaire and the Beliefs about Medicine Questionnaire will be assessed for each participant as part of the implementation / feasibility aims of the overall study.

Medication Adherence (participant facing)

The questionnaire will be completed at Weeks 6 and 12 of the study, and it questions the participant about his / her ability to take the study medication.

Health Service Utilization (participant facing)

This form will be completed at Weeks 6 and 12, and it will help ask the participant to indicate the number of visits he / she has had with a general practitioner, emergency room, outpatient clinic or private specialist.

Concomitant Medication Form

Participants may have multiple corresponding concomitant forms (if they are on multiple medications), or they may have zero corresponding forms on record (if they are not taking any concomitant medications). These forms will be used to record all medications taken by each participant during the study period (baseline, 6 weeks, and 12 weeks). In REDCap, the Concomitant Medications form has been enabled as a "repeating instrument" to allow for more than one record per participant.

If a participant is on a concomitant medication at baseline, that medication will be documented accordingly on these forms, and every medication that is initiated during the course of the study thereafter will also be documented in a concomitant medications form.

If a medication is stopped and then restarted, the date that the medication was stopped will be recorded and the new start date will be added and a new form will be completed for that medication. If a medication is stopped and changed to a medication of the same class, the stop date will be recorded, and new entry will be recorded for the new medication.

In REDCap the Concomitant Medications are linked to the "Ad Hoc" event. Any new, changed, or stopped medications at any point in the study should be recorded on the paper CRF and added to the Ad Hoc event in REDCap. The following information will be collected for each medication:

- Medication (brand and generic names)
- Dose and unit
- Frequency
- Route
- Start and stop date
 - If the participant does not recall the exact month **and** day mark it as January 1st with the corresponding year.

- If the participant does not recall the exact day but remembers the month, mark it as the 1st day of the month that they provide.

Participant Status

Refer to Section 11 for a detailed description of this form, which is to be updated dynamically, each time a study team member makes contact with a (prospective) participant.

Protocol Violation

Refer to Section 12 for details of tracking protocol violations and definitions.

Drug Tracking

Refer to Section 9 for details on the drug tracking procedures. This form will also be updated at each study visit and is tied to the “Ad hoc” event within REDCap.

Form Tracking

The Form Tracking form was created to help study staff and those monitoring the data determine the initial source for relevant sets of fields and forms. For example, if a study participant completes consent via the eConsent framework versus in-person, the form will document that.

Adverse Events

The Adverse Events (AE) form will also potentially represent zero to many observations per participant. The AE CRF / eCRF will document details of each individual AE. Within REDCap, all AEs will be documented in a separate “arm” (called “AE”). **Refer to the instructions above for assigning Record IDs in the Main Assessments and the AE arms upon initial entry.**

6. PHYSICAL MEASUREMENTS

The following sections detail procedures for specific physical measurements. These procedures pertain to a specific field or set of fields within the forms listed above.

Measurement of Height (Medical History CRF)

The participant’s height will only be completed at the baseline visit and it will be measured in **centimeters** (cm).

- Ask the participant to remove his / her shoes and stand on the floor with his / her back to the measuring tape. When standing, instruct the participant to stand straight and as tall as possible with their arms loose to their sides, should relaxed, and feet together. The participant’s shoulders, heels, and buttock should be against the measuring tape on the wall.
- Ensure that the participant is looking straight ahead.
- Read the height to the nearest **cm**.
- Record the value to the CRF.

Measurement of Weight (Medical History CRF)

Weight will be measured only at the baseline visit in **kilograms** (kg).

- Ask the participant to remove his / her shoes, heavy items of clothing (jackets, etc.), and heavy items from his / her pockets.
- Instruct the participant to stand on the center of the scale with his / her hand by his / her sides. The participant’s weight should be evenly distributed on both feet.
- Instruct the participant to look straight ahead.
- Record the weight to the nearest **0.1 kg**.

Automated Office Blood Pressure and Heart Rate (Blood Pressure and Heart Rate CRF)

The **automated clinic BP from the previous 12 weeks** will be captured on this CRF at the baseline visit **to assess eligibility** for the study. Heart rate and research-grade BP will be measured during all study visits and will be recorded in the CRF. Refer to the table below from the study protocol for blood pressure thresholds in determining eligibility. The table shows the range of automated office (clinic) and research blood pressures for inclusion, as well as a comparison with the QUARTET protocol in Australia:

	SBP lower limit, mmHg	SBP upper limit, mmHg	DBP lower limit, mmHg	DBP upper limit, mmHg
Automated office (clinic) measurement within the last 12 weeks, untreated	140	179	90	109
Automated office (clinic) measurement within the last 12 weeks, on monotherapy	130	159	85	99
Research grade blood pressure measurement in QUARTET Australia	No limit	No limit	No limit	No limit
Research grade blood pressure measurement (baseline mean)	115	None	60	None

A SBP or DBP level higher than these thresholds would lead to ineligibility. However, if an individual were eligible based on an in-range SBP or DBP level (i.e., isolated systolic hypertension or isolated diastolic hypertension), then a lower DBP or SBP would not lead to exclusion.

If either or both mean research grade blood pressures were lower than the listed SBP and DBP thresholds, then the participant would not be eligible.

Materials

- Omron HEM 907 Automated Blood Pressure Monitor
- Omron Arm Cuffs
 - Small (17-22 cm)
 - Medium (22-32 cm)
 - Large (32-42 cm)
 - X-Large (42-50 cm)
- Measuring tape
- Case Report Form

Preparation:

- Be sure to take the blood pressure in a quiet room that has a desk and chair'
 - The participant's arms should be rested at heart level during seated blood pressure measurement'
- Plug the Omron Hem 907 monitor into a power socket and turn on'
- The blood pressure monitor will need to be pre-programmed in average (AVG) mode to countdown 300 seconds before automatically taking 3 BP/HR readings, separated by 60 seconds each, instructions for changing factory settings are detailed in the manufacturer-

supplied manual on page 10. You will only need to do this once; these settings will then be stored in the device memory for all subsequent measurements taken in 'AVG' mode.

- On the Omron device, ensure that the P SET knob is set to 'AUTO' and MODE knob set to 'SINGLE.'

Methods:

- Ask the participant to empty his / her bladder prior to the assessment.
- Ask the participant to switch off his / her phone and to ensure it is not in his / her pocket.
- Briefly explain the measurement procedure to the participant so he / she knows what to expect. Inform the participant that the results of the blood pressure testing will be discussed once all measurements have been taken.
- Manually check the participant's heart rate for rhythm.

First Visit (BP)

- Before any patient contact make sure to wash your hands as per Center for Disease Control (CDC) guidelines.
- Measure the participant's arm circumference on both arms while he / she is standing.
 - Ensure that the measurement is taken on the middle of the arm between the shoulder and the elbow while the arm is in a relaxed position.
 - These measurements should be made directly on the participant's skin and NOT over layers of clothing.
- Select the proper sized cuff and secure around the participant's left bicep.
 - The cuff should be placed directly on skin if possible.
 - NOTE: The cuff should be placed approximately 3cm (or the width of two fingers) above the crease of the inner elbow. The tubing should exit at the lower side of the cuff and the arrow marked "ART." should be pointed over the middle of the inner elbow (over the brachial artery).
- Ensure that the cuff is connected.
- Instruct the participant to take a seat at the desk and make sure that his / her legs are not crossed and that both of his / her arms are rested at heart level.
- Ask the participant to stay quiet during the BP measurement and to avoid coughing.
- Turn the Omron HEM 907 OB Monitor ON. The monitor will display a zero on the screen.
- Turn the monitor away from the participant to ensure he / she cannot see the results.
- On the Omron device, ensure that the P SET knob is set to "AUTO" and MODE knob set to "SINGLE".
- After 5 minutes of quiet seated rest start the measurement of BP/HR on the left bicep. Record the value.
- While the participant is still seated, remove the BP cuff from the participant's left arm and place on RIGHT bicep, again ensuring the arrow marked "ART." is pointed over the middle inner elbow and tubing exits at the lower side of the cuff.
- Take the BP / HR reading on the right arm by pressing the "Start" button and record the value noting which arm has been identified in having a higher SBP.
- Record the higher SBP arm in the CRF, this arm will be used for all follow-up office BP measurements.

All Visits (BP)

- Before any patient contact make sure to wash your hands as per CDC guidelines.

- Attach the BP cuff to the arm that has been identified in having the higher SBP (moving the cuff back to the left arm if required).
 - The cuff should be placed directly on the participant's skin, approximately 3cm (or the width of two fingers) above the crease of the inner elbow (over the brachial artery).
- Change the MODE knob to “SINGLE” then take a single BP reading and record systolic and diastolic BP and heart rate in the CRF.
- Make sure the Omron HEM 907 device is pre-programmed in average (AVG) by changing the MODE knob to “AVG”. Pressing the START button will initiate to countdown 300 seconds before automatically taking 3 BP/HR readings, separated by 60 seconds each.
- Remind the participant to keep quiet, stay still and avoid coughing during the BP / HR measurements.
- Press the 'start' button, turn the monitor away from the participant to ensure he / she cannot see the results and leave the room. The device will automatically count down 300 seconds (5 minutes) before taking 3 measurements in 60 second intervals.
- Return to the room after 10 minutes.
- Press the GREY DEFLATION button and the 1st systolic, diastolic and heart rate will be displayed as per below images. Scroll down and press again for the 2nd, again for 3rd and again for average systolic and diastolic blood pressure and heart rate and record all four measurements in the CRF (see Figure, next page).
- If an 'ERROR' message is displayed on the screen you will need to re-start the BP/HR measurements using the Omron HEM907 device, including the 5-minute rest period.
- **NOTE:** In the rare event that a participant has a severe BP reading (SBP $\geq$ 180, DBP $\geq$ 120) inform a clinician at the health center immediately.

Measurement of 24-Hour Ambulatory BP Monitor

- The ABPM will be used at two separate time points during the study
 - Baseline
 - 12 weeks
- The participants should try wearing the device for 26 hours, targeting a full 24 hour recording on each occasion.
- **The guideline for ensuring participants meet inclusion / exclusion criteria regarding adherence to ABPM procedures will be as follows:**
 - The lower limit of hours of recording is 20 hours, with readings from at least 70% of the times a recording was attempted.
 - **minimum of 20 hours** of total recordings
 - **at least 70% of valid measurements within** those 20 hours of recordings
 - We are designating the hours: 22:00-06:00 as “nighttime” for this study. **At least six readings of the 20 hours recorded** should be within 22:00-06:00.
 - If there is any question regarding participant's eligibility based on adherence to ABPM, the study coordinator / research nurse will consult the QUARTET USA operations team for **consensus prior to enrollment**.
- Ensure new AA battery are put in to each machine

OSCAR 2 ABPM Set Up

Please refer to OSCAR 2 User Manual and Quick Start Guide

Equipment

- SunTech Oscar 2 ABMP AccuWin 4 software

- Ambulatory blood pressure monitors calibrated as per manufacturer's instructions
- BP cuffs
 - Wash between patient usage per instructions in user manual
- AA batteries
- Pouch with shoulder strap or belt
- Patient information and diary sheet

AccuWin 4 Installation

- You can install the SunTech AccuWin pro 4 ABPM Software on your computer two different ways:
 1. Visit www.suntechmed.com/software to request a copy of the software be e-mailed to you
 2. Through the Flash drive
 - a. Insert supplied flash drive into proper USB computer port
 - b. Open the flash drive content on your computer
 - c. Run the .exe file to start the installation of your software

Equipment Preparation

- Ensure all ABPM equipment is present and ready to use
- Before any patient contact make sure to wash your hands as per CDC guidelines
- Format the monitor with patient details and program the monitor with study specific parameters
- Inflation frequency should be set 30 minutes during daytime, 60 minutes nocturnally
- Set the monitor to hide the results from each measurement
- Set maximum inflation to the category 30-40mmHg above the office systolic measure to reduce risk of bruising.

ABPM Fitting

- Use a permanent marker to mark the brachial artery position on the patient's non-dominant arm with a cross
- Use an appropriately sized cuff (See table below)
- Connect the hose from the cuff to the monitor
- Position the hose comfortably on the patient ensuring the hose is not kinked. Drape the hose over the patient's shoulders, across the back of the neck and over to the contralateral side of the body; refer to the instruction manual for visual.
- Put monitor into its pouch. Attach the pouch to the patient using a shoulder strap or belt.

Table: Oscar 2 ABPM cuff sizes based on arm circumference. *Source: SunTech Oscar2 user guide*

Oscar2 ABPM Cuff Size	Arm Circumference Range
Size 2 Cuff	26-34 cm
Size 3 Adult Plus Orbit Cuff	32-44 cm
Size 4 Large Adult Orbit Cuff	42- 55 cm

Patient Instruction and Information

- Provide the participant with appropriate information, a diary sheet, and organize a time for the participant to return the machine
- Provide a verbal explanation of the following information:
 - Leave the monitor on for 26 hours

- Monitor operation – inflation frequency, repeat attempts for readings starting / stopping a measurement
- Avoid movement during cuff inflation
 - the patient should let the cuffed arm hang loose, no flexing of the elbow or moving the hand and fingers
- Cuff position – the arterial marker on the cuff should align with the brachial artery indicator (drawn cross)
- Monitor care – avoid getting the monitor wet (ensure the participant is instructed to avoid having a shower / bath whilst wearing the monitor), avoid twisting / kinking hose, avoid powders / other substances, do not drop monitor
- Turning the monitor off – if the monitor causes extreme pain or the participant wishes to discontinue the test, he / she may turn off the monitor and remove the cuff
- Participants should be instructed to document what they were doing during cuff inflation along with the time. They should also be encouraged to log their sleeping and awake time and the time that they took their medication
- Provide a contact phone number for questions or inquiries

Data Retrieval and Reporting

- Turn the machine on, plug it into a computer, and open the AccuWin program
- Click retrieve data, ensure patient details are correct
 - Confirm sleep and wake time with patient/diary
- Click 'Statistics' tab, check awake mean SYS (SBP) ≥ 135 mmHg or mean DIA (DBP) ≥ 85 mmHg (for screening purposes). Record these numbers in the CRF
- Print a copy of the report and keep in the participant file, results will be provided to the participants provider at end of study
- The AccuWin ABPM database will be extracted at the end of the trial. Ensure the database is regularly backed up to prevent loss

ECG

An ECG or AliveCor Kardia-Mobile Personal EKG will be performed at the health center during the baseline visit by the study nurse. If the participant has had an ECG within the past three months, he / she will not be required to complete one at the baseline visit. The study provider will interpret the ECG or AliveCor Kardia-Mobile Personal EKG tracing. A paper copy of the ECG or pdf of the AliveCor Kardia-Mobile Personal EKG will be kept in the participant's folder and will be scanned via media manager and will be uploaded into Epic and REDCap for the study providers to review.

Bradycardia Procedures

- Baseline visit:
 - All participants will be required to have an ECG obtained at baseline unless they have had an ECG available for review in the past 3 months.
 - Patients with asymptomatic sinus bradycardia will be eligible for inclusion (note: a heart rate less than 50 beats per minute would require discussion among study and clinical providers to confirm eligibility).
 - If the participant's ECG or AliveCor Kardia-Mobile Personal EKG demonstrates no conduction system abnormalities confirmed by the study physician, then the participant will be eligible for inclusion.
 - Conduction system abnormalities will be defined as evidence of sinus pause greater than two seconds, second degree atrioventricular block or greater, and trifascicular block.

- The treating provider can also determine that the patient may not be eligible for participation because of other conduction system abnormalities (e.g., first-degree atrioventricular block), but this would be captured through a separate exclusion criterion.
- At any point in the study, any participant with symptoms concerning for bradyarrhythmia or bradycardia (HR <60 bpm) will undergo an ECG or AliveCor Kardia-Mobile Personal EKG at subsequent visits (e.g., 6-week and 12-week follow-up visits), **which will be reviewed by the study physician.**
- 6-week follow-up visit for participants undergoing follow-up ECG or AliveCor Kardia-Mobile Personal EKG: all ECGs or AliveCor Kardia-Mobile Personal EKGs will be reviewed by a study physician, and the study team suggests those reviewing ECGs or AliveCor Kardia-Mobile Personal EKGs consult the guidelines below:
 - If a participant's HR is **at least 50 beats per minute** (bpm) in the **absence of symptoms / abnormalities noted on ECG**, then the participant can continue to take the study medication.
 - Otherwise, the study nurse / study physicians should contact the participant's primary care provider and determine if the participant should stop the study medication based on collective clinical judgement. For example:
 - If the participant's HR <60 bpm in the **presence** of symptoms, conduction system abnormalities, or both, then the study physician / participant's provider may want to consider stopping the study medication for that participant.
 - If the participant's HR <50 bpm in the **absence** of symptoms and conduction system abnormalities, then the participant may continue to take the study medication; however, the study physician / primary care provider should determine if the participant should continue medication based on their clinical judgement.

12-Lead ECG Instructions

- Ensure that the ECG machine is in the study room
- Perform hand hygiene per CDC guidelines prior to patient contact
- Explain the procedure and ask the patient to change into a gown
- Place the participant in the supine position with all limbs supported
- Place the ECG machine with power cord away from the participant
- Prepare the participants skin for application of disposable electrodes using alcohol wipes to cleanse and scissors as needed for body hair
- Firmly apply 4 limb electrodes first
 - Arm tabs downward
 - Legs tabs upward
- Locate proper chest electrode placements and firmly apply 6 electrodes with tabs facing downwards
- Connect lead wires to electrodes using color coding and abbreviations on alligator clips to ensure proper lead to proper electrode
- Connect participant cable into ECG machine and place cable on participants abdomen or table
- Turn on the machine and remind the participant to remain still, breath normally, and to not talk
- Follow the manufacturer's instructions to complete the ECG

- When complete, disconnect the lead wires and remove electrodes and wipe the skin as needed
- Perform hand hygiene
- Scan ECG into media manger in Epic

AliveCor KardiaMobile Personal EKG Instructions

(Source: <https://www.alivecor.com/previous-labeling/kardia/08LB12.3.pdf>)

- Clean the two electrodes on the KardiaMobile device with an alcohol-based sanitizer
- Launch the Kardia phone app
- Select 'Standard EKG'
- Rest two or more fingers on the KardiaMobile electrodes
 - The participant's right hand and fingers should contact the right electrode or the electrode closest to the bottom of the smartphone
 - The participant's left hand should contact the left electrode or the electrode closest to the top of the smartphone
- When the recording is complete, an analysis of the EKG will be available
 - Tap 'Save' to continue
- To email a pdf of the EKG recording for physician review, the study team member will tap the envelope icon next to the EKG on the Journal screen and tap email
 - The email: QUARTETSAFETY@LISTSERV.IT.NORTHWESTERN.EDU will be available on the study smartphone to the research nurse and study coordinator, which includes the study team physician responsible for reviewing ECGs prior to randomization
- The emailed pdf will be uploaded into media manager in Epic
- A pdf copy of the EKG will be printed and placed in the participant's folder

7. LABORATORY PROCEDURES

All laboratory testing and services undergone for purposes of the QUARTET USA study will be handled directly by LabCorp. At the ACCESS Martin T. **Russo** Family Health Center **lab draws will be completed by LabCorp personnel**. At the ACCESS **Ashland** Family Health Center **lab draws will be completed by ACCESS personnel**. Access Community Health Network has a long-standing relationship with LabCorp as their laboratory services meet good clinical practice (GCP) standards for high-quality and reliable testing.

Study team members will identify the specific laboratory panels that a participant will need to have completed one day prior to his / her study visit via Epic. The designated study physician will review the laboratory panels and electronically sign-off on the laboratory orders, releasing and handing over the request electronically to LabCorp and its designated phlebotomy staff. Upon completion of study visit assessments, either the study nurse or study coordinator will accompany the study participant to the phlebotomy room to have the participant's blood drawn.

Given the communication workflow between the Epic system and LabCorp system, the phlebotomist or medical assistant will review the open laboratory orders and identify the respective vacutainers to commence the blood draw process. The phlebotomist will follow standard clinical guidelines leading up to the blood draw procedure. Once the blood has been drawn, the phlebotomist or medical assistant will label each individual vacutainer with a respective barcode to identify the specimen by the individual's medical chart number. After the blood has been collected, it will be spun using the

centrifuge on-site and prepared to be picked-up by LabCorp staff in a designated LabCorp vehicle. The specimens will be shipped to the designated LabCorp site for analysis. The identified laboratory panels are as follows:

CPT 001057	Uric Acid, Serum
CPT 303756	Lipid Panel, Serum
CPT 322000	Metabolic Panel (14) Comprehensive, Serum
CPT 005041	Hemoglobin, Whole Blood
CPT 004036	Pregnancy Test, Urine
CPT 140285	Albumin/Creatinine Ratio, Urine

After LabCorp has finalized processing the specimens, the results will be electronically entered into the participant's medical record and available for the either the research coordinator / nurse, study physician, or the participant's primary care provider to review. The laboratory results will form part of the participant's medical record indefinitely, but the relevant data fields will be entered according to protocol in the Laboratory Assessments CRF.

Blood and Urine Test

If these tests have been conducted within three months of the screening / enrollment visit they will not be required to be repeated at baseline. The serum blood will include sodium, potassium, chloride, bicarbonate, urea, uric acid, serum creatinine, alkaline phosphate, albumin, bilirubin, glucose, hemoglobin, AST, ALT, eGFR (note differing calculations for African Americans and non-African Americans), triglycerides, HDL, LDL, and total cholesterol. The urine test will include albumin, creatinine, UACR, and a pregnancy test.

- Pending labs will be ordered in Epic as "pending" by the study coordinator and research nurse and will be approved by the study providers.
- The samples will be taken at the health center by an in-house phlebotomist. Fasting prior to the lab draw will not be required for the participants.
- The samples will be stored after collection at the health center and will be picked up by LabCorp at 3PM and 9PM.
- The lab results will be available in Epic and will be reviewed by the study physician. Any abnormal or out of range results should be marked and noted for clinical significance. Follow-up and further lab tests may be required.
- If the laboratory cannot report on the blood sample the participant will be asked to repeat the lab test at the health center.
- NOTE: If the pregnancy test comes back positive, ensure that there is proper handoff to the participants primary care provider. The pregnancy test results should be sent to their provider via in-basket.

8. RANDOMIZATION AND BLINDING

As this is a double-blind trial, neither participants nor study staff interacting with participants will have access to treatment allocation codes. The only unblinded individuals on the study team will be: the study biostatistician (Ciolino), the data manager, and one back-up clinical co-investigator at Northwestern (Persell). Randomization will occur within REDCap. Prior to initiation of the study, the biostatistician will upload a pre-generate sequences of Drug Kit ID numbers, using the Randomization Module within REDCap.

Each kit number will correspond to a treatment arm. The list sequence numbers, kit numbers, and corresponding treatment codes will be created via external statistical software and stored in a .csv file with restricted access (to only unblinded team members) on NU “FSMResFiles” servers. The file path is within: \\fsmresfiles.fsm.northwestern.edu\PrevMed\Projects\Quartet_Stats. Randomization will not be stratified on any baseline variables and it will employ a randomly permuted block design with varying block sizes. The details of the algorithm used to generate the randomization sequence (e.g., block size or permutations) will not be disclosed on any study documents; however, the code may be made available after study completion. Documentation will be housed in the above file path and is subject to version control for the purposes of reproducibility.

The study biostatistician will send the randomization kit numbers to the drug manufacturer, Sharp Clinical Services Inc., for labeling and packaging. Thus, there will be individuals at the manufacturing company who will be unblinded. Since they are not a part of the study team, we view this as a low risk necessity.

Unblinding Procedures

The study participants will not be unblinded until after the study is completed (by all participants) and the study is considered closed. The reason for this is to conceal allocation sequences and prevent from potential deduction of the randomization sequence or recognition of any potential patterns. After the last participant completes his / her last study visit, and after primary analysis results have been shared with the study team, all study participants or their primary care providers will be contacted via a letter to indicate their treatment allocations.

The Data and Safety Monitoring Board (DSMB) as indicated in the Charter may be unblinded to review accumulating study data and assess for safety signals.

While we do not foresee the requirement for emergency unblinding within this study, if a participant has a AE whose resolution would depend on unblinding (i.e., knowledge of whether he / she received active control or LDQT), the following will occur:

1. The study / treating physician may contact the study staff to indicate this (research coordinator / research nurse) and initiate a chain of communication.
2. The coordinator / nurse will put the physician directly in contact with the study biostatistician (primary), the data manager (back-up), or the clinical co-investigator back-up (second back-up).
3. The DSMB chair will be notified of the incident immediately by the unblinded representative from the study team (biostatistician or one of the back-ups).
4. The representative will contact the physician directly (**excluding any other staff**) to indicate the allocation for that participant.
5. **Refer to the participant by his / her Record ID in all communication between study staff and the treating physician / DSMB regarding these incidents.**
6. The unblinding incident will be reported as Reportable New Information (RNI) to Northwestern University's IRB.

Decisions regarding withdrawal or exclusion of the study participant or any study staff thereafter will be made on a case-by-case basis with consult from the DSMB and IRB.

9. STUDY DRUG SUPPLY AND STORAGE

Dispensing of Study Medication to the Site

All study drug will be packaged, labeled, and shipped by Sharp Clinical Services Inc. The study drug will be housed at the clinical site(s) where study procedures will occur in a locked closet – separate from any other drug supply rooms or pharmacies. The study staff will keep a thermometer in this locked closet that will monitor minimum / maximum room temperatures to ensure the study drug is stored in stable environmental conditions according to the manufacturer recommendations (room temperature: 59°F-86°F) along with a log that will track daily temperatures.

Quantity of Drug Dispensed

Drug will be manufactured in multiple manufacturing campaigns. There will be multiple shipments of study drug to the site, and study staff (the research coordinator and nurse) will perform an inventory of drug supply monthly, at minimum. This will allow the study team to review accrual rates alongside inventory at the site and determine whether drug supply at the site is too low to accommodate projected enrollment.

Each participant's individual drug kit will contain two bottles with seven weeks of study drug in each bottle. Add-on therapy will be provided as a standalone bottle containing seven weeks of medication. Breaking the total drug supply into two bottles will protect against loss of study drug if participants do not return for their Week 6 visits. The additional week is to allow for flexibility in visit scheduling if needed. Study staff should make every effort to have participants return for their follow-up visits at exactly 6 week $\pm$ 7 days window. This will ensure participants do not run out of study drug.

Dispensing Directly to Participants

Once the study staff member obtains a participant's drug kit number from REDCap, he / she will:

1. Locate the corresponding kit number in the drug inventory at the site.
2. He / she will mark the kit number on the paper Randomization CRF as documentation of the appropriate dispensation of study drug.
3. The study staff member must only dispense one bottle of study drug from that kit number at baseline.
4. The study staff member must sort that kit into a separate "pile" / shelf / area at the site within the closet space to indicate that the kit number is "active". There will be another bottle of study drug plus add-on therapy in each of these active kits.
5. At the six-week follow-up visit, the staff member will locate that "active" kit number, and:
 - a. Dispense the second bottle of study drug from that kit to that same participant (this should be checked multiple times).
 - b. IF add-on therapy is required per protocol, dispense the add-on therapy and instruct the participant on taking this medication in addition to his / her study medication.
6. At each study visit, complete the Drug Tracking form (note: located in the Ad Hoc REDCap Event) to indicate drug(s) dispensed / returned / lost / stolen.
7. Study staff will sort "inactive" or returned study drug bottles / pills in a separate area within the closet space as well once a participant exits the study.

Drug Accountability

Drug accountability at the participant level will be monitored centrally through completion of the eCRF: Drug Tracking and generation of reports for this form. However, on-site monitoring visits will include an assessment of drug inventory and accountability at both the site level and the participant level. Sharp Clinical Services Inc. will provide documentation of shipments and drug kit numbers included in these shipments. These will serve as the study-wide accountability logs. The participant-

level accountability will be monitored via participant listings provided to the clinical research associate (CRA) in conjunctions with an on-site monitoring visit. The CRA plans for investigational product verification for a random sample of 25% of enrolled participants; any discrepancies / queries / violations at the participant level will be noted via the site visit report and within the Data Resolution Workflow query management system in REDCap.

Disposal and Destruction

All returned drug product and containers will be housed at the study site in a designated area or shelf within the storage closet. After drug accountability procedures have been completed by the CRA for these drug kits, unused product will be returned in batches to Sharp Clinical Services Inc. for disposal and destruction. Return will follow Sharp Clinical Services Inc. procedures for secure shipment.

10. ADVERSE EVENT REPORTING

Procedures for documentation and reporting of adverse events are described in the Adverse Event Reporting procedure.

11. PARTICIPANT STATUS

Individuals who are screened and determined to meet preliminary eligibility criteria based on the medical record / IS query will be scheduled to attend a baseline visit where they will be asked to conduct the full baseline assessment to determine eligibility to participate in the study. Upon that baseline visit, whether an individual decides to participate, meets eligibility criteria to participate in the study, or concludes his / her participation in the study, he / she will be given a Record ID in REDCap to track his / her progress. Participant status will be coded and updated any time the status changes. This form will always be marked as UNVERIFIED in the study electronic database until the participant exits the study.

The status' of participants will be documented and decided on a case-by-case basis by the research team; specifically, the decision remove participants or discontinue study medication will require the research team consensus.

The participant status (patstat) codes and brief explanations are as follows:

- Ineligible – An individual was determined to be ineligible to participate in the research study per the baseline assessment. Reasons for why an individual was deemed ineligible may include: individual declined to participate in the study during consent process, etc.;
- Pending randomization – participant partially completed baseline assessments, and study staff are awaiting laboratory / ABPM / ECG values to determine full eligibility prior to randomization;
- Actively enrolled – participant is actively enrolled in the study;
- Actively enrolled, no longer on study drug – participant is actively enrolled in the study, but due to the discretion of the clinical study team or a potential AE, the participant is no longer taking the study drug. The study team is still capturing participant's data through any follow-up visits. An example of this would be if a participant becomes pregnant after randomization; in this case, the participant would discontinue study drug, but the study team would continue follow-up.
- Lost to follow-up (LTFU) – participants will be considered LTFU if after three attempts over a one-month time frame the participant remains unreachable. Document contact attempts in the relevant fields on the Participant Status form.
- Participant withdrew consent – participant has explicitly requested to be withdrawn from the research study and has provided written request.

- Removed from study (investigator decision) – participant has been removed from the research study as decided by the study team or recommendation by the IRB to ensure patient safety.
- Deceased – written documentation of the deceased participant has been obtained either through the participant's medical chart, notification from his / her provider, or death certificate from the State of Illinois.
- Completed study participation – participant has completed all study visits and assessments, and no additional follow-up is required.

If a participant's status does not fall under one of these criteria, select 'Other' (and specify briefly) and notify the database management team if there are additional options required.

12. PROCOTOL DEVIATION AND VIOLATIONS

We will use the following definitions to determine protocol deviations and violations for this study. The following text is taken and adapted from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3487227/>

Protocol deviation. A protocol deviation occurs when, without significant consequences, the activities on a study diverge from the Institutional Review Board-approved protocol, e.g., missing a visit window because the subject is traveling. Not as serious as a protocol violation. These minor deviations are considered “non-critical”, and they will be monitored by the QUARTET USA study team via quality reports and remote monitoring procedures.

Protocol violation. A divergence from the protocol that materially **(a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare.** These violations are considered “critical” deviations. Examples of protocol violations may include the following:

1. Inadequate or delinquent informed consent
2. Inclusion/exclusion criteria not met
3. Unreported serious adverse events
4. Improper breaking of the blind
5. Incorrect or missing baseline assessments
6. Mishandled samples
7. Materially inadequate record keeping
8. Missed primary outcome data collection
9. Intentional deviation from protocol, Good Clinical Practice, or regulations by study personnel
10. Repeated protocol non-compliance

Protocol departures will be discussed with the study team at regular meetings, and classification of the departures as violations will be determined by study team consensus. Any reportable new information (RNI) will be reported to the Northwestern University IRB as indicated here:

<https://irb.northwestern.edu/process/reportable-new-information>.

Participant-level violations will be documented in the Protocol Violation CRF and reported to the IRB as appropriate. Study-level violations will be documented externally from the primary study database(s) and again reported to the IRB. At on-site monitoring visits, the CRA will review documented protocol violations (both study- and participant-level) and report any undocumented violations that he / she identifies during the visit via a site visit report.

13. DATA COLLECTION AND CASE REPORT FORMS

Refer to the Data Management Plan (DMP) for details on CRF development, general data collection workflow, and query development and resolution to ensure data quality.

14. QUALITY CONTROL AND MONITORING PROCEDURES

Refer to the DMP and DSMP for the quality control and monitoring procedures.

15. SITE CLOSE OUT

Refer to the Site Performance Plan (Section 3) regarding site evaluation and potential to close study site(s) prior to study completion. Briefly, sites will be closed: due to lagging recruitment or at the end of the trial. The DMP and DSMP contain information regarding locking the study database and closeout monitoring visits, respectively.

We plan to develop an in-depth study closeout checklist that will resemble the following:

www.nidcr.nih.gov/sites/default/files/2017-10/Site_Closeout_Visit_Readiness_Checklist_v20_1375.docx

Specific closeout procedures a study site will involve:

- Ensuring completeness and organization of:
 - Screening / enrollment logs
 - Training documents and logs
 - Drug kit documentation
 - Paper CRFs – both blank and completed for each participant at that site
- Review and consolidation of all participant files. After completion of this consolidation and organization, hard copy documents will be sent to Northwestern University. The logistics of this process will be coordinated by the study coordinator and research nurse in collaboration with the study team and ACCESS.
- All used / unused study drug medication will be returned to Sharp Clinical Services Inc. The research nurse and study coordinator will coordinate the shipment and communication to Sharp. Sharp will then dispose of all study drug per their internal SOPs.
- Site closeout visit as specified in the DSMP.

16. PUBLICATION AND DISSEMINATION POLICY

Refer to the Study Protocol and the DMP for details on results dissemination and data sharing, respectively.

