PROTOCOL TITLE:

Association between a Pharmacogenetic Algorithm to Predict Blood Pressure Therapy with Blood Pressure Response to Anti-Hypertensive Therapy.

PRINCIPAL INVESTIGATOR or FACULTY ADVISOR:

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N/A

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

Table of Contents

After completing your protocol, right click on the Table of Contents below and select "Update Field." If prompted, select "Update entire table." This will automatically update the protocol sections and page numbers for you. Do this also each time you modify your protocol after initial approval.

ABBREVIATIONS/DEFINITIONS

BP/Blood Pressure

STUDY SUMMARY

Study Title	**Association between a Pharmacogenetic Algorithm to Predict Blood Pressure Therapy with Blood Pressure Response to Anti-Hypertensive Therapy.**
Study Design	Retrospective Association Study
Primary Objective	To retrospectively assess the effectiveness of the use of a patient's genes to predict which hypertension therapy is successful: 1. Level of blood pressure control (<140/<90) 2. Change in blood pressure from baseline to control
Secondary Objective(s)	1. Number of medications needed to obtain control 2. Time to control 3. Number of office visits to control 4. Side effects from hypertension therapy 5. Hypertension associated adverse events during the course of treatment
Research Intervention(s)/Investigational Agents	Association between blood pressure control and genetic variants important in blood pressure regulation.
IND/IDE # (if applicable)	
Investigational Drug Services # (if applicable)	
Study Population	Hypertensive patients who have achieved BP control
Sample Size (number of participants)	Up to 2000
Study Duration for Individual Participants	Less than one day

1.0 Objectives

Purpose: To assess the effectiveness of the use of a patient's genes to predict which hypertension therapy is successful, as measured by:

1. **Level of blood pressure control (<140/<90)**
2. **Change in blood pressure from baseline to control**
3. **Number of medications needed to obtain control**
4. **Time to control**
5. **Number of office visits to control**
6. **Side effects from hypertension therapy**
7. **Hypertension associated adverse events during the course of treatment**

2.0 Background

1. Significance of Research Question/Purpose:

Hypertension is known to have a strong heritable component. Previous work has demonstrated that sons of hypertensive patients are more likely to be hypertensive when compared to sons of normotensive individuals. Additionally, monozygotic twins are more likely to share hypertension than dizygotic twins who are more likely than non-twin siblings to share hypertension. Each of these previous studies demonstrate that genetics plays a role in the development of hypertension. For each major class of drugs (diuretic, vasodilator, and β-blocker) the effectiveness rate ranges from 40-60%. Contrary to common belief, even a small ~10-20% of patients have an increase in blood pressure with a given anti-hypertensive medication. These effectiveness rates go far beyond adherence in that these previous trials have controlled for medication adherence. In addition to this controlled studies, epidemiologic data has demonstrated that 40% of patients who take their medication, as prescribed by their clinician, do not have their blood pressure under control.

Unfortunately, despite a significant impulse in the medical community to move towards an "individualized medicine" approach to patient centered treatment, the current clinical treatment strategy is based on a set algorithm which does not take into account individual patient differences. Rather, physicians are guided to choose a drug (one out of many options) in a given class of drugs and use that specific drug as a "first line therapy" (typically initiating with the diuretic class) and titrate that specific drug of choice to therapeutic dosage regardless of efficacy[2]. It is only after a prolonged course of treatment with that specific class of drug that clinical efficacy is determined (typically three months). At this stage, if clinical guideline goals for blood pressure have not been met, it is often recommended that the patient remain on the "first line therapy" whilst an additional drug from a different class of drugs (typically an Angiotensin converting enzyme inhibitor (ACE inhibitor) or Angiotensin II receptor blocker (ARB)) is added to the

pharmacologic regimen. Again, this drug is titrated to recommended therapeutic dosage and another prolonged course of treatment is initiated before clinical efficacy is determined (an additional three months – six months since initiation of treatment). If at this point, clinical guideline goals for blood pressure have not been met, a third drug from a third class of drugs (typically a beta-blocker) is added and the process is repeated (another three months – nine months from initiation of treatment). Further, if clinical guideline goals have continued to be elusive, the diagnosis of refractory hypertension is added and the process is reinitiated with a different combination of drugs, different classes of drugs, different drug options within a given class of drugs, different dosages, or all of the above. Thus, from the time of initial diagnosis and the start of treatment to the point in which blood pressure is adequately controlled may take anywhere from three months to well over one year. This trial-and-error standard of care is clearly not optimal.

The blood pressure panel created by Geneticure has been created to comprehensively assess seventeen common genetic variants in the liver (drug metabolizing enzyme) cardiac, vascular, and renal systems that can improve therapeutic guidance for the clinician based on known functional alterations of the protein through these genetic changes, as well as demonstrated effects of certain drug classes on these various genotypes. Based on this information, a clinician can guide therapy with knowledge specific to their patient, rather than "trial-and-error" based on population data and using drugs with least side effects initially.

1. Preliminary Data: *N/A*
2. Existing Literature:

Background

Hypertension (high blood pressure) is one of the most important preventable contributors to disease and death in the United States and represents the most common condition seen in the primary care setting[1,2]. According to the American Heart Association, approximately 78 million adults (1 in 3) living in the United States have hypertension with more than 5 million new diagnoses made each year[3,4]. Of these individuals, 82% are aware they have it, 75% are currently being treated for it, but only 52% have their blood pressure under control (thus, ~48% do not have adequate blood pressure control). Hypertension is known to lead to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. In fact, in 2009, high blood pressure was listed as a primary or contributing cause of death in ~350,000 of the ~2.4 million U.S. deaths (14% of all deaths). From 1999-2009 the number of deaths attributable to hypertension increased by 44%. In 2009, the direct and indirect economic burden on the United States health care system associated with hypertension was

estimated at $51 billion. With the advent of improved diagnostic techniques, increased rates of health care utilization and screening, and the increasing age of the population, a continual upward trend in this expenditure is expected. Because nearly two-thirds of the people living with hypertension worldwide reside in developing countries, providing optimal treatment at the lowest cost is critically important.

Hypertension is known to have a strong heritable component. Previous work has demonstrated that sons of hypertensive patients are more likely to be hypertensive when compared to sons of normotensive individuals. Additionally, monozygotic twins are more likely to share hypertension than dizygotic twins who are more likely than non twin siblings to share hypertension. Each of these previous studies demonstrate that genetics plays a role in the development of hypertension. For each major class of drugs (diuretic, vasodilator, and β-blocker) the effectiveness rate ranges from 40-60%. Contrary to common belief, even a small ~10-20% of patients have an increase in blood pressure with a given anti-hypertensive medication. These effectiveness rates go far beyond adherence in that these previous trials have controlled for medication adherence. In addition to this controlled studies, epidemiologic data has demonstrated that 40% of patients who take their medication, as prescribed by their clinician, do not have their blood pressure under control.

Unfortunately, despite a significant impulse in the medical community to move towards an “individualized medicine” approach to patient centered treatment, the current clinical treatment strategy is based on a set algorithm which does not take into account individual patient differences. Rather, physicians are guided to choose a drug (one out of many options) in a given class of drugs and use that specific drug as a “first line therapy” (typically initiating with the diuretic class) and titrate that specific drug of choice to therapeutic dosage regardless of efficacy[2]. It is only after a prolonged course of treatment with that specific class of drug that clinical efficacy is determined (typically three months). At this stage, if clinical guideline goals for blood pressure have not been met, it is often recommended that the patient remain on the “first line therapy” whilst an additional drug from a different class of drugs (typically an Angiotensin converting enzyme inhibitor (ACE inhibitor) or Angiotensin II receptor blocker (ARB)) is added to the pharmacologic regimen. Again, this drug is titrated to recommended therapeutic dosage and another prolonged course of treatment is initiated before clinical efficacy is determined (an additional three months – six months since initiation of treatment). If at this point, clinical guideline goals for blood pressure have not been met, a third drug from a third class of drugs (typically a beta-blocker) is added and the process is repeated (another three months – nine months from initiation of treatment). Further, if clinical guideline goals have continued to be elusive, the diagnosis of refractory hypertension is added and the process is reinitiated with a different combination of drugs, different classes of drugs, different drug options within a given class of drugs, different dosages, or all of the

above. Thus, from the time of initial diagnosis and the start of treatment to the point in which blood pressure is adequately controlled may take anywhere from three months to well over one year. This trial-and-error standard of care is clearly not optimal.

The blood pressure panel created by Geneticure has been created to comprehensively assess seventeen common genetic variants in the liver (drug metabolizing enzyme) cardiac, vascular, and renal systems that is being studied to see if it can improve therapeutic guidance for the clinician based on known functional alterations of the protein through these genetic changes, as well as demonstrated effects of certain drug classes on these various genotypes. Based on this information, a clinician can guide therapy with knowledge specific to their patient, rather than "trial-and-error" based on population data and using drugs with least side effects initially.

3.0 Study Endpoints/Events/Outcomes

1. Primary Endpoint/Event/Outcome:

To assess the effectiveness of the use of a patient's genes to predict which hypertension therapy is successful, as measured by:

1. Level of blood pressure control (<140/<90)
2. Change in blood pressure from baseline to control

2. Secondary Endpoint(s)/Event(s)/Outcome(s):

Blood Pressure control with respect to:

1. Number of medications needed to obtain control
2. Time to control
3. Number of office visits to control
4. Side effects from hypertension therapy
5. Hypertension associated adverse events during the course of treatment

4.0 Study Intervention(s)/Investigational Agent(s)

1. Description: A multigene panel comprised of genes with known functionality in the heart, vasculature, and kidney, that are known to influence BP. This study will be performed as a retrospective study on patients within the Fairview Health System. Patients will be those who have been previously diagnosed with hypertension and have a history of blood pressure control (<140/<90 for two consecutive office measures. The study will involve collection of a buccal swab (can be done at the patient's home, by the patient) and a clinical chart review of the patient's hypertension and medication history. From the buccal swab we will assess 18 SNPs in 11 genes (2) SNPs in ADRB1, (2)

SNPS in ADRB2, (1) in SCNN1A, (1) in ADD1, (2) in SLC12A3, (3) in WNK1, (1) in ACE, (3) in AGT, and (1) each in AGTR1, CYP2D6*4 and REN) with known functionality in the liver, heart, vasculature, and kidney.

2. Drug/Device Handling: The device used for sample collection is a buccal swab kit that gently removes cells from the inside of the cheek. The Geneticure kit contains two buccal brushes and two tubes of lysis buffer. The patient swabs their left cheek and deposits the end of the swab in the lysis buffer, then does the same for the right cheek. This swab is placed (by the patient) in lysis buffer (a small tube) and shipped to the study site, if collected off site. The swab is then shipped to the University of Arizona Genomics core facility for DNA extraction, quantification, and assessment of the genes listed above. The study is retrospective in nature and the DNA assessment will not influence prescribing, i.e. no drugs will be changed based on this analysis for the patients. No identifying information will EVER accompany the kit to the genetic testing facility.
3. IND/IDE: In-vitro diagnostic device and exempt from IDE.
4. Biosafety: N/A
5. N/A

5.0 Procedures Involved

1. Study Design: Retrospective analysis of association with DNA variants with pharmacotherapy used to achieve BP control.

General Flow of Activities:

1. Patients identified via UMN AHC-IE and sent recruitment letter, consent, survey and buccal swab kit via FRA's recruitment mailing process.
   a. An E-mail, Letter, survey information, are included along with this submission.
2. Subject collects buccal swab:

Using the collection kit consisting of two buccal swabs and two uniquely barcoded tubes the investigator, patient, or designee will remove the first buccal brush and scrape the brush end across the inside of a Subject's right cheek repeatedly (for five seconds using moderate pressure). The investigator, patient, or designee will place the brush end over the open buffer vial and press the opposite end of the swab stick to release the brush into the buffer and then close the vial. The process will be repeated on the left cheek. Each of the right and left cheek vial numbers must be recorded on the clinical review form and accountability log as right (R), or left (L).

3. The patients return completed consent, buccal kit, to Geneticure for sorting.
4. The signed consent form is sent to the PI (Dr. Pamela Phelps) and the buccal swab in lysis buffer is sent to the University of Arizona Genomics core facility for Genotyping.
   - All genotyping is performed in a blinded manner looking at 19 single nucleotide polymorphisms.
5. $30 sent to participant at the time the Geneticure team receives the buccal swab, consent, etc. The Geneticure team will perform any follow-up needed for participants who do not receive their payment, additional questions. Clinical questions will be forwarded to Dr. Phelps as the PI
6. Research team (Fairview pharmacy residents Danielle Walla and Krista Weaver) conducts chart review and abstracts data onto CRFs
7. CRFs sent to Geneticure

Specific Study procedures:

Screening

- Identify Potential Study Subjects through AHC. Refer to the Inclusion and Exclusion Criteria sections of this protocol for a complete list of eligibility criteria.
- Obtain Written Informed Consent either in-person or via mail. Each potential study participant must be given time to review the IRB-approved informed consent form, have his/her questions answered to their satisfaction and sign the form prior to any study procedures being performed. A subject will be given a copy of the informed consent form.
- Review Inclusion/Exclusion Criteria. The investigator and/or designee will review all criteria to determine if the subject is eligible for enrolment. Eligibility of all subjects must personally be confirmed by the Investigator and will be documented on the CRF.

Enrollment

- Assign Identification Number to Eligible Subjects.

Chart Review

- Record demographics, antihypertensive medical history and most recent blood Pressure. Data will be documented in the source document and recorded on the patient demographic form, including but not limited to the following:
  - Age
  - Sex

- Height
- Weight
- Race
- Ethnicity

(additional data for collection is included in the attachment entitled "metrics")

Specimen Collection

- Collect Buccal Specimen.

Subject Numbering

Subjects meeting the criteria for enrollment (and their specimens) will be identified by unique numbers that will be assigned sequentially by order of enrollment. The pre-assigned investigational site number will be prefixed with GCE and the identification number and separated by a hyphen (e.g., GCE-001etc.). Throughout the descriptions within the protocol the A swab will be referring to the swab that has originated from the right cheek, while the B swab will be that that has originated from the left cheek. To further clarify. Subject GCE-001 will be given two barcoded tubes. These barcode numbers should be recorded for each patient. These will also be recorded as originating from the right cheek (A) or left cheek (B).

At no time should any study paperwork or specimens be marked with the subject's name or any other traceable identifier except for the informed consent form, which is signed by the subject and kept at the site. At no time should the original (signed) or a copy of this form be collected by the Sponsor or its representative.

2. Follow-Up: Data will be collected for up to one year.
3. Individually Identifiable Health Information: a chart review will be performed to assess a patient's BP medication history. No personally identifiable information (Name, Address, date of birth) will be kept with the study document. The only individuals who will have access to a patient's chart will be Fairview clinical employees who also have IRB approval to be involved with this study. The linking information (from consent) will be kept in the PI (Dr. Pamela Phelps) office in a locked cabinet. No patient data with identifying information will be transmitted outside of the Fairview system. Additionally, no de-

identified PHI will be transmitted to any individual who does not have IRB approval to be involved with this research study.

4. Use of radiation*: N/A*
5. Use of Center for Magnetic Resonance Research*: N/A*

6.0 Data and Specimen Banking

If this study does not involve data or specimen banking for future use, type "N/A" and delete the sub-headings below. Otherwise, complete all items below.

1. Storage and Access: Data will be stored on secure, password-protected Fairview Health Services Servers.
2. Data: BP control history and relevant cardiovascular and side-effect data will be collected. We will not be banking any of this information for other studies, this is for the present study only.
3. Release/Sharing: No individual data or patient information will be released or shared with any individual who is not approved to participate in this research study.

7.0 Sharing of Results with Participants

1. We will share patient's genetic results, if requested. None of the genes are known to be major cancer causing genes. If we share the genetic results with the patient this will be done by a Fairview clinician on our research team. We will offer genetic counseling services, if the patient requests such a service. The laboratory where the genetic testing is performed (the University of Arizona Genomics core) is a CLIA-certified genetic laboratory.

8.0 Study Duration

1. *Describe:*
    - An individual will just need to provide two buccal swabs and complete a BP medication survey. This will take less than one hour.
    - We anticipate it will take approximately 6 months to recruit our subjects.
    - We anticipate it will take one year in total from beginning of study for data to be presented in abstract for and submitted as a manuscript.

9.0 Study Population

1. Inclusion Criteria:
    1. Subject is able and willing to provide informed consent
    2. Subject is ≥ 20 and ≤ 85 years of age

3. Subject with diagnosis of Hypertension for a minimum of 1 year
4. Subject has been on the same class/classes of blood pressure medication for a minimum of 6 months. Note: A change in dosage, frequency, or specific medication is acceptable as long as there have been no changes to the class/classes of medications prescribed.
5. Subject with a Body Mass Index (BMI) ≥ 19 and ≤ 45
6. Subject is currently prescribed and taking one of the following classes of medications alone or in combination with each other.
   - o Diuretics (thiazide or thiazide-like)
   - o ACE Inhibitors
   - o Angiotensin Receptor Blocker (ARB)
   - o Beta-blockers
   - o Ca+ Channel Blockers

2. Exclusion Criteria:

1. Subject has a diagnosis of secondary hypertension or is experiencing a complication of pregnancy.
2. Subject is currently prescribed and taking any additional class of medication(s) for high blood pressure not included in the list above
3. Subject has Systolic BP > 190 or Diastolic BP > 120 documented within the six months prior to visit.
4. Any other reason that the subject is inappropriate for study enrollment in the opinion of the Investigator.

2. Screening:

Because this is a retrospective chart review study, subjects will be screened by a Fairview employee (or AHC personnel) for eligibility. Only subjects who have opted in (or who have not opted out) of research will be contacted.

10.0 Vulnerable Populations

1. Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.

☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☒ None of the above

2. *Adults lacking capacity to consent and/or adults with diminished capacity to consent:*

   - *N/A*

3. Additional Safeguards: *If the research involves individuals Checked in Section 10.1 above, provide justification for their inclusion and describe additional safeguards included to protect their rights and welfare.*

   - *N/A*

11.0 Local Number of Participants

1. Local Number of Participants to be Consented: Up to 2000 subjects may participate in the study. 600 subjects are ideal for statistical analysis but given possible co-morbidities, we aim to consent up to 2000 individuals.

12.0 Local Recruitment Methods

1. Recruitment Process: Subjects will be recruited via letter, phone call, and e-mail (drafts of each are attached to the IRB ETHOS “smart” form)
2. Source of Participants: Medical record review
3. Identification of Potential Participants: Recruited based on inclusion/exclusion criteria, Fairview participation, and willing to participate in a research study. Participants will primarily be identified via AHC-CTSI data that is gathered daily for Fairview participants

who have not opted-out of research. In addition, we may also use the following reach-out methods:

- Dr. Phelps is a Fairview clinician
- Dr. Phelps via mailer.
- In the mailer (attached to the IRB) we ask the patient regarding approval of use of medical records. In addition to this we will not use any patient who has opted out of research within the Fairview system.

4. Recruitment Materials: Attached
5. Payment: 30 dollars for completion of the buccal collection and BP history survey (which is attached)

13.0 Withdrawal of Participants

1. Withdrawal Circumstances: The researchers may withdraw a subject if they have inadequate DNA yield, they have a severe co-morbidity that was not previously flagged, or if the participant does not submit their buccal swab.
2. Withdrawal Procedures: If a participant withdraws no data will be gathered after this time and no data from this participant will be used in the research. It is the patient's right to withdraw at any time.
3. Termination Procedures: N/A

14.0 Risks to Participants

For each risk or set of risks below, include the procedures to be performed to lessen the probability, magnitude, duration, or reversibility of those risks.

1. Foreseeable Risks: Although unlikely, there is a possible risk of knowledge of genetic information. Given that none of the genes we are assessing are severe disease causing genes we find this highly unlikely.
2. Reproduction Risks: N/A
3. Risks to Others: It is possible that family members will try to infer their genetic results based on those of the participant.

15.0 Potential Benefits to Participants

1. Potential Benefits: There are no direct benefits to the participants.

16.0 Data Management

1. Data Analysis Plan:

The Investigator is responsible to ensure the accuracy, completeness, and timeliness of reported data.

All data will be compiled within the Fairview system on secure servers. De-identified final data may be sent to Geneticure using a secure, password-protected Excel spreadsheet on a server that is only accessible to IRB-approved personnel and is fully auditable. The database will be validated prior to use in the study. All required data will be recorded on CRFs or paper facsimiles. Data collected within the CRFs will be supported by source documents as appropriate and may be updated to reflect the latest observations on the subjects participating in the study. Corrections to the source documentation will be made in a manner that does not obscure the original entry and will be dated and initialed by the Investigator or assigned designee. It is important for data entry to occur in a timely manner, therefore, data collected on source documents should be transferred into CRFs as soon as possible following study visits.

All data will be coded for statistical analysis (i.e. drug classes will be coded numerically and genotypes will be coded numerically). Subject's raw genetic data will be entered into the Geneticure for Hypertension algorithm. All data will be analyzed with SPSS v.20. Normality of the data will be assessed using Levene's test prior to statistical analysis and any correction for non-normal data distribution will be used. Descriptive statistics will be computed (average time for blood pressure control, average number of visits to the clinician for blood pressure control, age, height, weight, BMI, etc.).

Data will be initially analysed following the collection of samples/data from up to 600 subjects. Statistical tests will be corrected for the number of tests run (preservation of alpha). Ordinary least squares regression via univariate modelling will be used to estimate the magnitude of linearity between drug class that yielded the best blood pressure control and genetic profile of the subject. Multiple regression analysis will be performed to determine the impact of confounding variables (height, weight, age, race) on blood pressure control. For all statistical analyses an alpha level of 0.05 will be used to determine statistical significance.

Missing Data

All patients with available data will be included in the analyses of the study objectives. No patients will be directly contacted to retrieve missing data, and no sensitivity analyses will be performed on missing data.

2. Power Analysis:

Power Calculation and Sample Size:

Given the unique study design and pilot/feasibility nature of this proposal, highly accurate preliminary data are not available to generate detailed power calculations on the impact of the Geneticure panel for hypertension therapy. This is due to the lack of studies that have been performed in a prospective manner on genetic guidance for hypertension. However, previous work from our group utilizing a relatively small sample size and chart review have yielded data on all

17 genes that are contained within the Geneticure panel for hypertension treatment. Several of the genes with large effects can demonstrate statistical differences at relatively small sample sizes. For instance position 49 of the beta-1 adrenergic receptor demonstrates a functional genotype mean arterial blood pressure of 97mmHg (SD of 12.4mmHg) with beta-blocker therapy and the non-functional genotype demonstrates a mean arterial blood pressure of 102mmHg (SD of 11.5mmHg) with this same therapy. A power calculation based on this site of the beta-1 adrenergic receptor would yield a sample size per group needed of 109 for an alpha level of 0.05 and a power of 0.80 (not correcting for multiple comparisons) (table 1). Based on these results we can determine that the gene with the smallest effect from this previous smaller study (specifically that encoding WNK-1, rs2107614) will determine the approximate sample size needed to observe an effect, if an effect exists, for the panel as a whole in this prospective trial. Data from our phase-I trial demonstrates a mean arterial blood pressure of 97.6mmHg with diuretic therapy in the functional genotype group of WNK-1 and a mean arterial blood pressure of 100.8mmHg (Pooled SD = 12) with diuretic therapy in the non-functional genotype group for this site of WNK-1. Without correcting for multiple comparisons, one can determine that a per-group sample size of 162 individuals would be needed for 80% power with an alpha of 0.01. Using an alpha of 0.05 and a power of 0.80 we have estimated that we will need 300 subjects per group to observe a significant difference, where one exists. Based on possible retention of 70% of subjects who initially enroll, we will seek to recruit up to 2000 subjects for the study.

Concomitant Medications/Treatment/Procedures

This study protocol does not require change to any existing treatments or those prescribed during the course of the study by the Investigator or any other provider whom the subject sees for any medical reason. Outside of eligibility screening, there are no clinical evaluations planned as part of this study.

17.0 Confidentiality

1. Data Security: As mentioned previously, all data will be de-identified and stored on pass-word protected Fairview Health servers. The only linking information (the consent) will be kept in a locked cabinet in Dr. Pam Phelps office.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

- *N/A*

19.0 Provisions to Protect the Privacy Interests of Participants

1. Protecting Privacy: No identifiable information wil be kept, other than the consent document (which serves as the linking identifier) which will be kept in a locked cabinet in Dr. Pamela Phelps' office. We will only reach out to patients who have not opted-out of research within

the Fairview system. Only IRB-approved personnel with appropriate training (CITI, biomedical, etc.) will be interacting with these patients.

2. Access to Participants: If the subjects agree to participate in the study, have not opted out of research within the Fairview system, and the study is approved for us to access patients in the manner by which we propose in this IRB form and attached documents, we will have access to the patients using the techniques detailed herein.

20.0 Compensation for Research-Related Injury

1. Compensation for Research-Related Injury: *N/A*
2. Contract Language: *N/A*

21.0 Consent Process

1. Consent Process (when consent will be obtained):

The investigator will prepare an informed consent form in accordance with this study protocol and all regulatory requirements (21 CFR Part 50) using the template informed consent form provided by the sponsor. The informed consent form must be submitted to the IRB and a copy of the final IRB-approved consent form must be submitted to the investigative team prior to the start of the study at that investigational site.

Prior to any study procedures, all subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the IRB-approved Informed Consent Form. As part of the consent process, the subject will have the opportunity to ask questions of, and receive answers from the personnel conducting the study.

The investigator will notify the investigative team and the IRB within 5 working days if device use occurs without subject informed consent.

2. Non-English Speaking Participants: N/A

22.0 Setting

1. Research Sites: *Fairview Health System, Kasota Center* (virtual study: i.e. patients will not be coming in for visits)

23.0 Multi-Site Research

- N/A

24.0 Resources Available

1. Resources Available:
    - We have the full capability to complete this research. This is an accomplished research and clinical team that consists of experts in clinical care, physiology, pathophysiology, and

statistics. In addition, as needed, medical residents may help with data extraction if they are approved by the IRB.

25.0 References

1. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46.
2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama 2003;289:2560-72.
3. American Heart Association. Heart and Stroke Statistics - 2004 Update. In: Dallas: American Heart Association; 2004; 2004.
4. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-e220.
5. Akpunonu BE, Mulrow PJ, Hoffman EA. Secondary hypertension: evaluation and treatment. Disease-a-month : DM 1996;42:609-722.
6. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008;117:e510-26.
7. Johnson JA, Turner ST. Hypertension pharmacogenomics: current status and future directions. Curr Opin Mol Ther 2005;7:218-25.