Randomized, Placebo-controlled, Single Blind, Trial to Determine the Safety and Efficacy of Ticagrelor for Maintaining Patency of Arterio-Venous Fistulae Created for Hemodialysis.

NCT02335099

Version Date 19 Dec 2018

IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.

17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.
21. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Investigators Experience

Dr. Abdel-Rahman is the director of the Acute Kidney Injury-Therapeutic Extracorporeal Unit (AKI-TECU) that deals with dialysis-dependent AKI patients. He has been a Nephrologist for close to 25 years. He currently is a professor in the division of Nephrology. He is an established researcher with more than 40 peer-reviewed publications. His main area of research is related to improving outcomes of patients on hemodialysis

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator

Brief Summary/Abstract

This study is a randomized, placebo-controlled, single blind clinical trial. Seventy patients with ESRD on chronic HD and a functioning AVF will be recruited. Consent form will be obtained. History and physical, dialysis parameters and laboratory data (CBC, CMP, PTT & INR) will be obtained throughout the study. The following data will be documented on each patient: 1-Age/gender/race/body weight/cause of ESRD 2-Vintage of HD 3-Time since access was placed 4-Type and place of access and blood flow rate of access 5-History of prior access problems 6-Comorbid conditions (Hypertension, coronary artery disease, Diabetes Mellitus, Bleeding problems, peripheral vascular disease). 7-Current medications (Coumadin, Erythropoiesis stimulating agents, heparin, other antiplatelets, digoxin, statins). Patients will be randomized into two groups to receive: Group 1: Ticagrelor 90 mg PO BID Group 2: Placebo drug PO BID.

Subjects will have a screening visit and if they qualify for the study they will have 18 additional visits. All of these visits will occur while the subjects are at their normal dialysis treatment. Subjects will be randomized to either the Ticagrelor group or the placebo group. Subjects will be on study medication for 6 months then they will have a follow up period off drug for 6 months. Subjects will be seen twice a month while on study medication and once a month in the follow up period. While the subjects are on study medication we will assess any side effects of the study medication and put their relation to the study drug at each study visit. We will use clinical monitoring as suggested by Beathard (21). We will document the subject's adherence to the study, if they are hospitalized and what caused their hospitalization. A monthly intra-access flow will be obtained using ultrasound dilution by transonics as part of standard of care. Any change in the clinical assessment of the access, prolonged bleeding (>20 minutes) after removal of needles, trend of decreasing intra-access blood flow as determined by transonic (> 25% or original flow), or an access flow rate < 400 ml/min, will prompt a referral for a fistulogram. If confirmed stenosis (>50% stenosis of the access diameter) an intervention (angioplasty) will be performed. This intervention is part of the subject's standard of care.

Background

1. Provide the scientific background, rationale and relevance of this project.

The main renal replacement therapy for End stage renal disease (ESRD) in the USA is hemodialysis (HD). Vascular access for hemodialysis can be provided by means of an autogenous fistula, arteriovenous graft, or central venous catheter. The autologous brachio-cephalic (Brescia-Cimino) fistula remains the access of choice, since its patency and rate of infection are superior to those made of exogenous material once early failures are excluded (1). A functioning vascular access is crucial for HD. However, vascular-access failure (VAF) is common and is a major source of complications (1). Complications of the vascular access, particularly stenosis and thrombosis, continue to remain the Achilles' heel of HD therapy and lead to extensive morbidity in HD patients. VAF is the most common reason for hospitalization among HD patients (2-4). The economic burden of

VAF is estimated at greater than 1 billion dollars per year (1) and continues to grow. Recent data have suggested a significantly high incidence of inflow stenosis of vascular access (14–42%) in this patient Population (5-7). Hence, guidelines were adopted for adequate monitoring and surveillance of the vascular access as well as criteria for adequate evaluation and timing intervention (8). Surveillance of an access is done by dynamic or static methods. Dynamic intra-access flow measures, by many methods as duplex doppler ultrasound, magnetic resonance angiography, and ultrasound dilution by transonics), are among the preferred methods of AV access surveillance (8). Patients with VAF are referred for evaluation and treatment if access flow rate <400-500 mL/min, in the presence of continuous persistent abnormalities in the surveillance parameters or a prospective trending drop of the access blood flow rate (8). There is no consensus in the literature as to the use of anticoagulants or antiplatlets for arterio venous fistula prophylaxis. . Multiple studies aiming at thromboprophylaxis to prevent VAF were done using various antiplatelet agents (Ticlodipine (9-12), Dipyridamole (11, 13, 14), Aspirin (15, 16) and Clopidogrel (17-19) showing variable results. While Sreedhara et al (13) showed that Dipyridamole can be thromboprophylactic for new arterio-venous graft (AVG), it failed to show any benefit to previously stenosed grafts. Dixon et al. (14) using extended release Dipyridamole in addition to aspirin, showed modest, though significant, decrease in AVG stenosis. Clopidogrel decreased thrombotic graft episode (18) but was reported to be associated with increased bleeding (17). Ticlodipine was used alone (9, 10, 21) or with Dipyridamole (11) to study its role in maintaining the patency of arterio-venous fistula (AVF) with controversial results.

Ticagrelor (Brilinta) is a new drug approved for use in patients with acute coronary syndrome to reduce the rate of thrombotic cardiovascular events. Early studies (please see investigator brochure for more information) showed that Ticagrelor achieves a higher inhibition of platelet aggregation as compared to Clopidogrel. The primary route of Ticagrelor elimination is via liver metabolism, thus, does not require dose adjustment in patients with renal impairments. Since Ticagrelor has not been used in hemodialysis patients for the purpose of preventing thrombosis in dialysis vascular accesses (Arterio-Venous Fistulae and Grafts), this study is designed as a pilot study to evaluate the feasibility and safety of Ticagrelor in hemodialysis patients with AVF vascular access to see if the treatment efficacy of Ticagrelor can preserve patency of hemodialysis vascular access better than Placebo.
Objectives: The primary objective is to evaluate the feasibility and safety of Ticagrelor in hemodialysis patients with AVF vascular access. The secondary objective is to evaluate the treatment efficacy in that whether Ticagrelor will preserve patency of hemodialysis vascular access better than Placebo. Hypothesis: Ticagrelor is safe and will preserve patency of hemodialysis vascular access (Arterio-Venous Fistulae) better than Placebo

The drug Ticagrelor, approved by FDA for patients with ACS, was never tested in patients with ESRD. In addition, if proven safe and effective in maintaining the patency of vascular access in patients with ESRD, which will be a new indication for the drug and hopefully will help, patients with ESRD maintain the patency of their access

Hypothesis to be Tested

Hypothesis: Ticagrelor is safe and will preserve patency of hemodialysis Arterio-Venous Fistulae better than Placebo. This is a Randomized, Placebo-controlled, Single Blind clinical trial. Seventy patients with ESRD on chronic HD and a functioning AVF will be recruited. Consent form will be obtained. History and physical, dialysis parameters and laboratory data will be obtained. Patients will be randomized into two groups to receive: Group 1: Ticagrelor 90 mg PO BID Group 2: Placebo drug PO BID Patients will be seen twice a month while on study treatment. We will assess any side effects and the relation to the study drug. -Clinical monitoring -Document adherence to the study -Document hospitalization with cause. -A monthly intra-access

flow will be obtained using ultrasound dilution by transonics which is a standard of care procedure. Any change in the clinical assessment of the access, prolonged bleeding (>20 minutes) after removal of needles, trend of decreasing intra-access blood flow as determined by transonic (> 25% or original flow), or an access flow rate < 400 ml/min, will prompt a referral for a fistulogram. If confirmed stenosis (>50% stenosis of the access diameter) an intervention (angioplasty) will be performed. This intervention is part of the study patient's standard of care. Timeline of study: -6 Months recruitment phase -6 months active study phase: -6 months follow up: both groups will be monitored by complete physical examination, laboratory and dialysis data as well as monthly transonic assessment of intra-access blood flow rate will be done for standard of care and we will document if any intervention is required. -6 months statistical analysis and data documentation

Objectives: The primary objective is to evaluate the feasibility and safety of Ticagrelor in hemodialysis patients with AVF vascular access.
The secondary objective is to evaluate the treatment efficacy of Ticagrelor to see if it will preserve patency of hemodialysis vascular access better than Placebo.

Study Design: Biomedical

1. Will controls be used?

Yes

►IF YES, explain the kind of controls to be used.

Yes, we will have a group of study subjects that will be given a placebo in addition to what they would get that is the current standard of care for their medical issue.

2. What is the study design?

This is a randomized, placebo-controlled, single-blind study.

3. Does the study involve a placebo?

Yes

►IF YES, provide a justification for the use of a placebo

The placebo group can be used as an "add on" to standard of care in comparison to an investigational treatment added to standard of care. This is what will happen in this study.

Human Participants

Ages: 18 to 85
Sex: Male and Female
Race: All
Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol.

70

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

25%

3. How many subjects will be enrolled at all sites?

88

4. How many subjects will sign a consent form under this UVa protocol?

88

5. Provide an estimated time line for the study.

We hope to have enrollment completed within 6 months of protocol approval.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Patients on chronic hemodialysis with a functioning arterio-venous fistula
- Subjects must agree to use adequate contraception to prevent pregnancy

2. List the criteria for exclusion

- Hemoglobin less than 9g/dL per chart review of the last Hemoglobin level obtained for standard of care.
- If the study subject can't be washed off of anti-coagulants or antiplatelets
- Recent history of bleeding over the last 3 months preceding enrollment
- History of bleeding disorder (hemophilia, Von Willebrandt disease, etc….). Anemia only if it is chronic and thrombocytopenia if the platelet count is consistently <125,000.
- Recent history of blood transfusion over the last 3 months preceding enrollment
- Recent serious injury or surgery over the last 3 months preceding enrollment
- History of gastro-intestinal ulcers
- Moderate-severe hepatic impairment (ALT/AST greater than 3-5 times the upper limit of normal).
- Uncontrolled blood pressure (SBP> 190 or DBP >110) pre or post dialysis
- History of stroke within the last 5 years.
- Pregnant females-self reported
- Hypersensitivity to Aspirin /antiplatelets
- Subjects using peroral anticoagulants
- History of intracranial hemorrhage
- Active pathological bleeding
- Hypersensitivity to ticagrelor or any component of the product

3. List any restrictions on use of other drugs or treatments.

Subjects using peroral anticoagulants will be excluded to avoid excessive bleeding risk. There will be a 4 day wash off for subjects who are taking anticoagulants and anti-platelets. If subjects can't be washed off of these medications then they cannot be included in the study.

Statistical Considerations

1. Is stratification/randomization involved?

Yes

►IF YES, describe the stratification/ randomization scheme.

Every other study subject will be on active study drug. Investigators and study personnel will be un-blinded.

►**IF YES, who will generate the randomization scheme?**
__X__UVa Statistician: Jennie Ma

2. What are the statistical considerations for the protocol?
Since Ticagrelor has not been used in hemodialysis patients for the purpose of preventing thrombosis in dialysis vascular accesses (Arterio-Venous Fistulae and Grafts), this study is designed as a pilot study in that patients are randomly assigned to receive Ticagrelor or placebo drug for a six-month treatment period plus an additional 6-month follow-up period. The primary objective is to evaluate the feasibility and safety of Ticagrelor in hemodialysis patients with AVF vascular access. The secondary objective is to evaluate the treatment efficacy in that whether Ticagrelor will preserve patency of hemodialysis vascular access better than Placebo. The study will follow intent-to-treat principle and all randomized patients will be included in the analyses for the primary and secondary objectives.

3. Provide a justification for the sample size used in this protocol.
Due to the pilot nature of this study, formal power analysis and sample size estimation is not essential. Nevertheless, we attempted to estimate the potential treatment efficacy in this study. We considered the outcome measure for efficacy evaluation is the time to first stenosis event during the study period. From our recent clinical data, it was estimated that approximately 36% of dialysis patients experienced stenosis event at one-year follow-up. We would expect that patients in the new drug arm would have 10% stenosis event rate at one-year follow-up, compared to the 36% stenosis event rate in the placebo group. With these considerations, the analysis of stenosis-free survival will require at least 21 events, which is the number of events needed for one-sided log-rank test at 5% significance level to have 80% power to show statistically significant difference when the true hazard ratio is 0.236. This estimation will result in that approximately seventy patients will be needed and evenly randomized into each study arm (35 patients in Ticagrelor and 35 in placebo). This is an open-label study. Upon completion of all the required screening assessments, eligible patients will be randomly assigned to the study drug or placebo at 1:1 ratio with a block size of 20 in accordance with the randomization schedule. The randomization schedule will be provided by the Department of Public Health, School of Medicine. Patients will be identified by unique subject identifier that will remain consistent for the duration of the study. The active study period is 6 months followed by 6 months of monitoring, and accrual rate is approximately 12 patients per month. To compensate for an estimated drop-out rate of 25%, we will recruit 88 patients to the study.

4. What is your plan for primary variable analysis?
We have recruited/consented a total of 54 subjects into this study. We have enrolled a total of 43 patients into the study, 23 in the Ticagrelor treatment arm and 20 in the placebo arm. We will evaluate the safety of Ticagrelor in hemodialysis patients with AVF vascular access by tabulating adverse events and severe adverse events for the two study arms, and the difference between the two arms will be tested by chi-square test.

5. What is your plan for secondary variable analysis?
For the secondary outcome, i.e., time to the first stenosis event, we will compare stenosis-free survival of Ticagrelor versus placebo using the Kaplan-Meier method. Survival probabilities and corresponding 95% confidence interval (CI) will be calculated at landmark time points for each arm, and survival difference between the two arms will be evaluated using a one-sided log-rank test stratified by the history of stenosis. Further, a stratified Cox proportional-hazards model will be used to derive the hazard ratio and 95% CI between the two regimens.

6. Have you been working with a statistician in designing this protocol?
Yes

IF YES, what is their name?
Jennie Ma

Biomedical Research

1. What will be done in this protocol?

Subjects will be in this study for 1 year. Up to eighty eight patients with ESRD on chronic HD and a functioning AVF will be enrolled. For statistical purposes we will need to have seventy people complete the study. Consent form will be obtained. History and dialysis parameters will be taken at the screening visit. At the screening visit we will also be collecting a serum sample to perform a pregnancy test on female subjects of child bearing potential. This will be collected in a 3.5ml gold top serum separating tube. Study participants will be on the study medication (Ticagrelor) or placebo for six months (Visit 1 to Visit 12). Subjects will take the study medication twice a day. They will take it once in the morning and once in the evening. We will also instruct them to try and take it around the same times each day if possible. We will be collecting study medication to check for compliance at Visits 3, 6, 9, and 12. There will be a follow up for these subjects for six months (Visit 13 to Visit 18). Subjects will have a physical performed at screening, visit 12 (this is the last visit when subjects are on medicine), and at visit 18 which is the end of the study. We will be looking at hemoglobin levels that are collected as standard of care two times a month. We will be collecting the bleeding time weekly as well. This will be done at all visits (screening to Visit 18) which we define as the time it takes for a subjects' access to stop bleeding.

The following data will be documented on each subject at screening:
1-Age/gender/race/body weight/cause of ESRD
2-Vintage of HD
3-Time since access was placed
4-Type and place of access and blood flow rate of access
5-History of prior access problems
6-Comorbid conditions (Example: Hypertension, coronary artery disease, Diabetes Mellitus, Bleeding problems, peripheral vascular disease).
7-Current medications (Example: Coumadin, Erythropoiesis stimulating agents, heparin, other antiplatelets, digoxin, statins)
This data will be obtained from the dialysis computer system and will be verified with the subject.
8-Physical Exam
9-Vital signs (blood pressure, heart rate, and weight) will be obtained from the subject's dialysis record.

Adverse events and concomitant medications will be reviewed at each study visit. We will also note any access issues at each study visit.

Study Medication Stopping Rules for Prolonged Bleeding:
If post treatment bleeding time is prolonged more than 30 minutes we will stop the study drug and refer for fisulogram,
If bleeding still persists after fistulogram and intervention we will continue to hold the study drug and do work up for bleeding. We will continue to hold study drug for 5 days if signs of increased tendency for bleeeding as recurrent Epistaxis > twice in one week, if any evidence of GI bleed, or if Hgb should drop > 1gm in one week. If the bleeding is believed to be drug related or it no resolution occurs the subject will be withdrawn from the study.
We will also hold study drug for 5 days if hemoglobin is consistently less than 8g/dL for 2 consecutive weeks, or hemoglobin dropping 1g/dL in one week.

For a prolonged bleeding event standard practice will be applied, including: (prolonged bleeding is defined as bleeding more than 30 minutes)

- **Direct pressure.** Any bleeding that warrants an emergency department visit should be immediately controlled with the application of direct digital pressure to the puncture site for 5-10 minutes. Once the bleeding abates, the patient should be observed for rebleeding or early thrombosis for 1-2 hours.
- **Gelatin sponges.** Commonly seen in the emergency department as Gelfoam®, this adjunct may aid in the hemostasis of bleeding AV grafts. Although studies or case reports of this material being used in this setting are not found in the medical literature, our clinical practice has demonstrated success by including it in the management of this problem.

Life-Threatening Bleeding From Hemo Access

A vascular surgeon should be emergently consulted if hemorrhage cannot be quickly controlled. An adjunctive suture may be placed if there appears to be a small laceration of the graft rather than a puncture wound. This suture is used only after other measures to control bleeding described above have also failed.

Other life threatening bleeding: Subjects will be sent to the emergency department

2. Will you be using data/specimens in this study that were collected previously, with the use of a research consent form, from another research study?
No

3. List the procedures, in bullet form, that will be done for research as stipulated in this protocol.

- Physical Exams
- Administration of Investigational Drug
- HcG Blood Pregnancy Test
- Collection of Bleeding Time

Note: Laboratory data will be captured and recorded for research purposes from blood collected as part of the subject's clinical care-no additional blood is collected for the purpose of this study.

4. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding?
Yes

►**IF YES,** ***check one of the following two options:***

__X__The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

- The PI takes full responsibility for the identification of incidental findings:
- The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.**
- A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic**.**

5. Do any of the procedures listed above, under question # 2, utilize any imaging procedures (e.g. ultrasound, CT scans/ x-rays etc.)? **If yes, LIST PROCEDURES: No**

6. Will you be using viable embryos? No

7. Will you be using embryonic stem cells? No

Specimens

Specimen Information

1. Describe the type of specimen to be used:

Answer/Response: At the screening visit only, we will collect a 3.5ml gold top serum separating tube from women in the study who are of child bearing potential.

2. Will the specimen be obtained BEFORE a subject has signed a consent form?

IF YES, or if consent or documentation of consent is waived and the specimen is identifiable per HIPAA regulations, the research team will be required to track this disclosure with Health Information Services.

Answer/Response: No

3. Will you be using discarded specimens?

Answer/Response: No

Answer the following two questions as it pertains to ALL blood being drawn for this study.

►IF NO, and taking a blood sample, will blood be taken more than 2 times/week?

Answer/Response: No

►IF NO, and taking a blood sample, check the option(s) below which match the subject population.

_____ healthy, non-pregnant adults who weigh at least 110 pounds.
_____ Amount will NOT exceed 550 cc in an 8 week period
_____ Amount to exceed 550 cc in an 8 week period

__X__ Non- healthy or pregnant adults and/or children
__X__ Amount will NOT exceed the lesser of 50ml or 3 ml/kg in an 8 week period
_____ Amount will exceed the lesser of 50 ml or 3 ml/kg in an 8 week period

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen?

Example: name, date of collection, subject # medical record#

Answer/Response: Name, Date/Time of Collection, Subject MRN#

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label?

Answer/Response: No

3. Will any additional data be linked to the specimen by way of a code?

Example: name, date of collection, subject # medical record# , diagnosis, clinical information

Answer/Response: No

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected?

INSTRUCTIONS: This question does not refer to a specimen that is collected for long term tissue banking, but rather analysis that is already described in the protocol.

Answer/Response: Yes

Specimen Shipping

1. Do you plan to ship any specimens outside of UVA?

Answer/Response: No

Data and Safety Monitoring Plan

If you have any questions completing this section call 982-4311, 924-8660 or 243-9847 for assistance
A Sponsor is defined as entity that will receive data prior to publication.

1. Definition:

1.1 How will you define adverse events (AE)) for this study?

__X__An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects.

1.2 How will you define serious adverse events?

__X__A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an unanticipated problem?

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.

- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What is the definition of a protocol violation?

Do not change this answer

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

_____ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

__X__ Unanticipated Problems- will follow Unanticipated Problem recording and reporting procedures outlined in section 3.

1.6 What is the definition of a Protocol Enrollment Exception?

__X__NA- No outside sponsor

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What are **identified risks and plans to minimize risk**

**Please Also Refer to the Investigator Brochure and the Package Insert for Brilinta/ Ticagrelor

Adverse Events with Brilinta/Ticagrelor

Frequent complaints (seen in at least 3% of study participants) that have been reported during studies:

- Bleeding
- Dyspnea (Shortness of Breath)
- Cough
- Dizziness
- Nausea
- Atrial Fibrillation (Heart Rhythm Disorder)
- Hypertension (High Blood Pressure)
- Non-Cardiac Chest Pain

- Diarrhea
- Back Pain
- Hypotension (Low Blood Pressure)
- Fatigue
- Chest Pain
- Headache

More Frequent complaints (seen in at least 6 to 7% of study participants) that have been reported during studies:

- Bradycardia (Slow Heart Rate)
- Elevated Serum Creatinine

There have also been cases of increased uric acid levels for subjects taking ticagrelor. A high uric acid level, or hyperuricemia, is an excess of uric acid in your blood. Uric acid is produced during the breakdown of purine, a substance found in many foods. Once produced, uric acid is carried in your blood and passes through your kidneys, where most of it leaves your body when you urinate. A high uric acid level may result in attacks of gout, but not everyone who has high uric acid gets gout, and not everyone with gout has high uric acid. Increased uric acid may also increase the chances of kidney stones. There is also an increased risk of severe bleeding for subjects taking ticagrelor. Due to the increase risk of severe bleeding there may be a risk of delay in any surgery that you may need while taking this study medication.

Expected Risks related to study participation.	**Frequency**
Reproductive Risks These are unknown at this time.	Minimized due to the requirements of this protocol.
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed that will minimize risks to participants:

- Study personnel will be checking on patients twice a month for six months while subjects are on study treatment and once a month while subjects are in the follow up visits.
- We will be monitoring the time it takes for the subject's access to clot.
- AE monitoring at each visit
- Weekly Hemoglobin Tests

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

__X__At subject, PI or sponsor's request

__X__Treatment would be stopped if the subject had a serious adverse event deemed related to study

__X__ Subjects will be stopped if they meet one or more of the study stopping rules

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

These are called stopping rules for early termination of the entire study.
List criteria regardless of whether the study is sponsored or not.
Be sure to include any criteria for which the UVa PI would halt the study at UVa.

__X__Per IRB, PI, DSMB, or sponsor discretion

2.5 What are the criteria for breaking the blind/mask?

__X___NA – Not blinded/masked

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__X__IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded?
No

►IF NO, what criteria will be used?

__X__Only adverse events that are deemed related AND serious

3.2 How will adverse event data be collected/recorded?

__X__Paper AE forms/source documents

3.3. How will AEs be classified/graded?

_____World Health Organization Criteria (WHO)

_____NCI Common Toxicity Criteria, Version 2.0/ NCI Common Terminology Criteria, Version 3.0

_____NCI CTCAE Version 4.0

__X__Mild/Moderate/Severe

__X__Serious/Not serious

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__X__The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__X__After subject begins study drug/ device placement/intervention /study-related procedure/specimen collection

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

_____End of study drug/device/intervention/participation

_____30 days post study drug/device/intervention

__X__Subject completes intervention and follow up period of protocol

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, related and Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the enrollment exception.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*

Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

UVa PI HELD IND			
Type of Event	**To whom will it be reported:**	Time Frame for Reporting	How reported?
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

Reporting of serious adverse events

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.
When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal

investigator. Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229.Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.
In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.
All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca on a quarterly basis preferably using the MedDRA coding language for serious adverse events.

4. **How will the endpoint data be collected/recorded.**
   _____Protocol specific case report forms

   __X__Source documents

5. **Data and Safety Oversight Responsibility**

   5.1. Who is responsible for overseeing safety data for this study ?

   __X__No additional oversight body other than PI at UVa Skip question 5.2

   5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor? N/A

   5.3. What items will be included in the aggregate review conducted by the PI?

   __X___All adverse events

   _X____Unanticipated Problems

   _X____Protocol violations

   _X____Audit results

   _____Application of dose finding escalation/de-escalation rules

   These should be outlined under 2.4.

   _____Application of study designed stopping/decision rules

   _____Early withdrawals

   _X___Whether the study accrual pattern warrants continuation/action

   _____Endpoint data

   5.4 **How often will aggregate review occur?**

   For additional information on aggregate review see:
   www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

   __X__Annually

   5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?

A copy of these reports must be sent to the IRB if applicable as soon as they are received by the PI. Do not wait until the next continuation to submit them to the IRB.

__X__NA- PI is the overall person overseeing the safety data for this study.

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__X__Part of IRB-HSR continuation status form

Payment

What is the difference between compensation and reimbursement?
A reimbursement is used when the subject is paid back for travel expenses such as mileage, lodging, food while traveling. Receipts or mileage must be submitted for a reimbursement.

Compensation is "payment" for things such as time, discomfort, inconvenience.

Total possible compensation should reflect the true value of the total possible dollar amount per participant for one year involvement in the study whether it be cash, check, gift card, goods, etc. or a combination of these items.

Retention "Gifts"- gifts may be given to a subject periodically during the study to remind them they are in the study. Sponsors may provide such items as water bottles, birthday cards etc. to the subject. NOTE: Cash or gift cards are NOT allowed as retention items.

1. Are subjects being reimbursed for travel expenses (*receipts /mileage required***)?**No

2. Are subjects compensated for being in this study?
Yes

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$415.00

2b. Explain compensation to be given.

- For the screening visit subjects will be compensated $25.00 due to length of time necessary to complete this visit.
- For the first 6 months of study participation, when subjects are on ticagrelor or placebo (visit 1 to visit 12) subjects will be compensated $25.00 for their time in completing these visits.
- For the last 6 months of study participation, when study subjects will **not** be taking ticagrelor or placebo subjects will be compensated $15.00 for their time in completing these visits.

2c. Is payment pro-rated (*e.g. some compensation is given even if subjects do not complete the entire study)?*
Subjects will be compensated for all visits that they complete.
If No, explain why payment cannot be pro-rated.

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa?

Yes

2d(i). How will the researcher compensate the subjects?

__X___Check issued to participant via UVA Oracle or State system

2d(ii). Which category/ categories best describes the process of compensation?

__X___ All compensation will be made via check issued to participant via UVA Oracle or State system

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

The main renal replacement therapy for End stage renal disease (ESRD) in USA is hemodialysis (HD). A functioning vascular access is crucial for HD. However, vascular-access failure (VAF) is common and is a major source of complications. Complications of the vascular access, particularly stenosis and thrombosis, continue to remain the Achilles' heel of HD therapy and lead to extensive morbidity in HD patients. VAF is the most common reason for hospitalization among HD patients. The economic burden of VAF is estimated at greater than 1 billion dollars per year and continues to grow.

Ticagrelor (Brilinta) is a new drug approved for use in patients with acute coronary syndrome to reduce the rate of thrombotic cardiovascular events. If Ticagrelor is shown to be safe and is efficacious in preserving patency of hemodialysis vascular access (Arterio-Venous Fistulae) better than Placebo, it will be an addition to our armamentarium that and will improve patients' lives, quality of lives as well as a potential big impact on lowering the cost burden of HD patients, by avoiding frequent interventions to restore patency to a stenosed AVF.

2. Do the anticipated benefits justify asking subjects to undertake the risks?

The drug, Ticagrelor (Brilinta), is FDA approved for patients with acute coronary syndrome and thus has an acceptable safety profile. The potential benefit of the drug such as minimizing the interventions for stenosed AVF, decreasing hospitalization for fistulae-related admissions, outweigh the potential risk. Safety precautions such as frequent monitoring of the patients by the Principal Investigator and obtaining periodic laboratory data will minimize any potential risks

Bibliography

1- Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. J Am Soc Nephrol 7:523–535, 1996

2-US Renal Data System: Excerpts from the USRDS 1999 annual data report. Am J Kidney Dis 34:s40–s62, 1999

3- Woods JD, Port FK: The impact of vascular access for haemodialysis on patient morbidity and mortality. Nephrol Dial Transplant 12:657– 659, 1997

4- Winsett OE, Wolma FJ: Complications of vascular access for hemodialysis. South Med J 78:513—517, 1985

5-Beathard GA, Arnold P, Jackson J, et al., Physician Operators Forum of RMS Lifeline. Aggressive treatment of early fistula failure, *Kidney Int*, 2003;64:1487–94.

6-Khan FA, Vesely TM, Arterial problems associated with dysfunctional hemodialysis grafts: Evaluation of patients at high risk for arterial disease, *J Vasc Interv Radiol*, 2002;13:1109–14.

7-Asif A, Gadalean FN, Merrill D, et al., Inflow stenosis in arteriovenous fistulas and grafts:A multicenter, prospective study, *Kidney Int,* 2005;67:1986–92.
8-http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_uptoc.html
Accessed 9/1/13
9- Gro¨ntoft KC, Mulec H, Gutierrez A, Olander R. Thromboprophylactic effect of ticlopidine in arteriovenous fistulas for haemodialysis. Scand J Urol Nephrol 1985; 19:55-7
10- Gro¨ntoft KC, Larsson R, Mulec H, Weiss LG, Dickinson JP. Effects of ticlopidine in AV-fistula surgery in uremia. Scand J Urol Nephrol 1998; 32: 276–83.
11-Yevzlin AS, Conley EL, Sanchez RJ, Young HN, Backer BN. Vascular access outcomes and medications use: a USRDS study. Semin Dial 2006; 19: 535
12- Fickerstrand CE, Thompson IW, Burnet ME, Williams P, Anderton JL. Double-blind randomized trial of the effect of ticlopidine in
arteriovenous fistulas for hemodialysis. Artif Organs 1985; 9: 61–3.
13-Sreedhara R, Himmilfarb J, Lasarus JM, Hakim RM. Anti-platelet therapy in graft thombosis: results of a prospective, randomized, double-blind study. Kindey Int 1994; 45: 1477–83.
14-Dixon BS, Beck GJ, Vazquez MA et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. N Engl J Med 2009; 360: 2191–201.
15-Kooistra MP, Van Es A, Marx JJM, Hertsig MLA, Struyvenberg A. Low-dose aspririn does not prevent thrombovascular accidents in low-risk haemodialysis patients during treatment with recombinant human erythropoietin. Nephrol Dial Transplant 1994; 9:
1115–20.
16 Andrassy K, Malluche H, Bornefeld H et al. Prevention of p.o. clotting of av. Cimino fistulae with acetylsalicyl acid. Results of a prospective double blind study. Klin Wochenschr 1974; 52: 348–9.
17-Kaufman JS, O'Connor TZ, Zhang JH et al. Randomized controlled trial of clopidogrel plus aspirin to prevent hemodialysis access graft thrombosis. J Am Soc Nephrol 2003; 14: 2313–21.
18- Trimarchi J, Young P, Forrester M, Schropp J, Pereyra H, Freixas E. Clopidogrel diminishes hemodialysis access graft thrombosis. Nephron Clin Pract 2006; 102: c128–32.
19-Dember LM, Beck GJ, Allon M et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis. A randomized controlled trial. JAMA 2008; 299: 2164–71.
20-Coleman CI, Tuttle LA, Teevan C, Baker WL, White CM, Reinhart KM. Antiplatelet
agents for the prevention of arteriovenous fistula and graft thrombosis: a meta analysis.
CI Int J Clin Pract 2010; 64 (9):1239-1244,
21-An algorithm for the physical examination of early fistula failure Semin Dial 2005 18(4):
331-335

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual as they are not allowed by UVa Policy*
- *All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.*
- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures whether those procedures are experimental or standard.*
- *The IRB cannot grant clinical privileges.*
- *Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.*
- *Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.*
- *Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.*

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- *No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*
- *No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.*

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.

1. **How do you plan to <u>identify</u> potential subjects?**

   To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
   If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.

   a. _X___ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or quality improvement.

      DHHS: Study team requests Waiver of Consent to identify potential subjects.

      HIPAA- *Allowed under Preparatory to Research if PHI to be accessed.*

      IMPORTANT
      Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
      - *a UVa student working in the UVa HIPAA Covered Entity**
      - *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

   b. ____ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

      DHHS: Study team requests Waiver of Consent to identify potential subjects.
      HIPAA- *Allowed under Preparatory to Research if PHI to be accessed.*

      IMPORTANT
      Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
      - *a UVa student working in the UVa HIPAA Covered Entity**
      - *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

      NOTE: The information from which you are obtaining potential subjects must also have an IRB protocol approval.

      IRB# _____

      If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797.

   c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients knowledge.

      DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA- *Allowed under Preparatory to Research if PHI will be shared by the health care provider.*

IMPORTANT

Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

d. ____ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating.
DHHS: *NA*
HIPAA: *Allowed under Health Care Operations*
If this choice is checked, check 3d-INDIRECT CONTACT below.

e. ____ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.
If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: *NA*

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.
IRB# of registry/ database: _____
DHHS & HIPAA: *NA*

If item # a, b or c is checked above and if this protocol involves the use of protected health information you confirm the following to be true:

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

Yes

2. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

a.____Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

b._X___Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

You should share the following information with the potential subject:

1. *Your name*
2. *Who you are:* ***physician, nurse etc***. at the University of Virginia.
3. *Why you want to speak with them*
4. *Ask if you have their permission to explain the study to them*
5. ***If asked about how you obtained their information use one of the following as an option for response.***
   - ***DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN:*** *Your doctor, Dr.* ***insert name*** *wanted you to be aware of this research study and gave us permission to contact you.*
   - *We obtained your information from your medical records at UVa**.*** *Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.*

   IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c._X___Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
***HIPAA:** Allowed under Health Care Operations.*

d.____ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

***DHHS & HIPAA:** NA*

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.
If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

3. **Will any additional information be obtained from a potential subject during "prescreening"?** No

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** No

5. **How will the consenting process take place with either the prospective subject, the subject's legally authorized representative or parent/legal guardian of a minor (if applicable)?**
Patients who appear to meet inclusion/exclusion criteria (chart pre-review), and also, express interest in participation, will be approached by an investigator or study coordinator to discuss the informed consent process. Unless the patient states preference to review the document the day of initial contact, then a copy of the informed consent document will be provided to the patient, and arrangements made for the coordinator or investigator to meet the patient at a future date/time to review the document. Patients will be encouraged to take the consent home to share with family members, and also instructed to write down any questions they wish to have addressed. The meeting to review the document will take place at a time designated as convenient by the patient. Each section of the informed consent document will be reviewed with the patient, and the consent reviewer will solicit questions from the patient. After discussion and agreement from the patient to

participate, then he/she will sign the informed consent. The research team member obtaining consent will sign the document, too. Patients who consent will be given a copy of their signed informed consent. The consent process will be documented.

6. Will subjects sign a consent form for any part of the study?
Yes

7. Will the study procedures be started the same day the subject is recruited for the study?
No

8. Is there the potential to recruit economically or educationally disadvantaged subjects, or other vulnerable subjects such as students or employees?Yes

If yes, what protections are in place to protect the rights and welfare of these subjects so that any possible coercion or undue influence is eliminated?
Study staff will inform the subject that participation is voluntary and choosing not to participate will not affect their care, their status as a student or employee at UVA.

9. Do you need to perform a "dry run" of any procedure outlined in this protocol?
No

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?
Drug Name: Ticagrelor (Brilinta) and Placebo, Manufacturer: Astra Zeneca
IND exempt notification from FDA on file

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?
Emaad Abdel-Rahman, MD

3. What is the phase or stage of this study?
Pilot

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?
Brilinta® (ticagrelor)

2. Where will the subjects be seen for the administration/dispensing of the drug?
__X___ Outpatient Unit: *specify:* The study drug will be given to dialysis patients at their regularly scheduled dialysis treatment on the 5th floor of the West Complex in the Dialysis Unit

3. What dose will be utilized in this study?
Brilinta® (ticagrelor) - 90mg

4. What will be the frequency of dosing in this study?
Twice a day

5. What will be the duration of dosing in this study?
6 months

6. What route of administration will be utilized?

Oral

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?

_____ YES
__X__ NO- Drug will be prepared and/or administered per package insert

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?

No

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.?

No

10. How will missed doses be handled?

If a subject misses a dose we will document the missed dose and the subject will not replace the dose that was missed.

11. Will a comparator (active or placebo) be utilized in the protocol?

Yes

►IF YES, comparator is:

__X___ Placebo*:* The placebo medication will be identical in appearance to the active study medication.

12. Does this study involve research on a drug, biologic, supplement or food additive?

Yes

►IF YES, is this study investigator initiated?

If yes, answer questions # 13 and 14
If no, answer question # 13 only.

Yes

13 Are you using a drug/supplement/food additive in a manner not approved by the FDA?

Yes

IF YES, answer questions 13a-13f
You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

See section 1 and section 4 of the investigator brochure

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

See section 1 and section 14 of the investigator brochure

13c. Have there been any human deaths associated with this drug?

No

13d. In how many humans has this drug been used previously?

This is an approved drug for use in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction)

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.

N/A

14. Do the following criteria apply? *Check all that apply*

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

__**X**__ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

__X__ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and *This item must be checked.*

__**X**__ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

15. Is this a post-marketing study?

No

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1a-1e) to describe your/central registry's plan to protect the identifiable data from improper use and disclosure.

1a. How will data be stored?

__X___ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.

1b. Will specimens be stored by the UVa study team? No

1c. Will any of the data be stored electronically by the UVa study team?

Yes

►IF YES, will it include any HIPAA identifiers with health information or other highly sensitive data?

►IF YES, where will it be stored?

__X___ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA.

1d. Will any of the data be collected or stored in hard copy format by the UVa study team (*e.g.- on paper*) ? Yes

►IF YES, where will it be stored?

__**X**___ case report forms will be stored in a secure area with limited access.

1e. The following procedures will also be followed.

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential.
- Each investigator will sign the University's Electronic Access Agreement forward the signed agreement to the appropriate department as instructed on the form.
  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection. Identifiable data is considered to be "Highly Sensitive". A Limited Data Set is usually considered to be "Moderately Sensitive" and de-identified data is usually considered to be "Not Sensitive".
- If identifiable data (*data with health information and HIPAA identifiers*) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and UVa Institutional Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data *is:*
-personal information that can lead to identify theft if exposed or
-health information that reveals an individual's health condition and/or history of health services use.

PHI- *a type of Highly Sensitive Data, is health information combined with a HIPAA identifier*

- LIMIT- Limit the HIPAA identifiers to the minimal amount needed- e.g. use initials instead of name, use a code instead of initials, limit amount/type of health information collected, and collect and share only those items you state you will in this protocol.
- SECURE- Secure Highly Sensitive Data
  - Because single-use electronic devices and media, such as desktops, laptops, memory sticks, CDs, smartphones etc., can be easily lost or stolen, the University strictly limits the circumstances under which Highly Sensitive Data may be stored on them. In accordance with the University's Electronic Storage of Highly Sensitive Data Policy, you must obtain written approval from your Department AND VP or Dean prior to moving data to single use devices or media by using the Highly Sensitive Data Storage Request Form.
    - *You additionally are responsible for applying all security safeguards covered in that policy, including but not limited to password protecting and encrypting any document on a single access electronic device.*
    - *If you use your smartphone to send email and your phone is not managed was not purchased and/or set up for you by the Health System, you cannot send Highly Sensitive Data via email.*
      - *In addition, do not use Outlook Web to send your email if it contains sensitive data.*
      - *Also, you are not allowed to auto forward your email to outside email systems like Gmail or Yahoo.*
      - *Do not save any email attachment containing Highly Sensitive Data to a single use device.*
    - *You are allowed to access Highly Sensitive Data stored on the University or Health Systems network via a VPN, however you cannot download any of the information onto your desktop or laptop.*
    - *Store files containing Highly Sensitive Data on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the "F" and "O" managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive.*
    - *If data will be collected and/or viewed via a website, it is critical that the website and associated data file are set up in a highly secured manner. Do not attempt without assistance from:*
      University Side: ITCmicrosystems@virginia.edu
      Health System: Web Development Center: (434-243-6702)
  - Encrypt any electronic file containing Highly Sensitive Data that is not on a network drive specifically designated for this purpose. . *See encryption solutions guidance.*
  - Password protect any electronic device containing Highly Sensitive Data.
  - Lock up hard copies of Highly Sensitive Data.
- PROTECT- Protect Highly Sensitive Data
  - Do not leave a hard copy file open on your desk when not using it and secure your computer when not attended.
  - Have discussions in private.
  - If you lose Highly Sensitive Data, you must report it in accordance with the Information Security Incident Reporting Policy.

- Do not share Highly Sensitive Data with those not on the study team or those who do not have a need to know.
- Do not share with sponsor unless subject has already signed a consent form or IRB has approved waiver of consent.
- If faxing Highly Sensitive Data within UVa
  - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
  - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
- If faxing Highly Sensitive Data outside of UVa to the sponsor or CRO after the subject has signed consent:
  - the receiving fax machine is in a restricted-access location,
  - the intended recipient is clearly indicated,
  - the recipient has been alerted to the pending transmission and is available to pick it up immediately.
  - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
  - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
- Highly Sensitive Data may not be stored in a Drop Box.
- If you plan to store data in the Cloud, you must consult with UVa Information Technology Services (ITS) to verify all essential security measures are in place. If you have a contract to use the cloud, the contract must include required security measures as outlined by ITS.
- DO NOT email health information with name, medical record number or Social Security number to or from an email address that does not have an *HS in the address. May use subject initials if within the UVa HIPAA covered entity: The "UVA HIPAA covered entity" includes the hospital, health system, School of Medicine School of Nursing and the VP for Research Office.
- Be aware: PHI collected without consent/ HIPAA authorization will NOT be allowed to leave UVa in an identifiable form unless the disclosure is tracked with Health Information Services.
- Any Highly/Moderately Sensitive Data sent outside of UVa (e.g. to sponsor) that was obtained under a consent must be encrypted and password protected.
- If your electronic device is sent outside of UVa for repair, all institutional data, whether Highly Sensitive or not, must be either encrypted or removed.
- If transporting Highly/Moderately Sensitive Data in paper format from one UVa building to another, take the following steps to protect it:
  1. Put paper inside a closed container such as a briefcase, or sealed envelope to limit the chance of a losing a piece.
  2. Do not leave Highly Sensitive Data unattended in a public area if it is not locked up.

- When the study is complete, all electronic files containing Highly/Moderately Sensitive Data must be stored on a network drive specifically designated for that purpose. They may not be stored on a single use device such as a CD.

- STOP, THINK and BE CAREFUL-
  - If this was your Highly Sensitive Data how would you want it protected?
  - There are significant monetary fines to the individual and the institution for loss or misuse of sensitive data.
  - Your job may also be on the line.

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

__X__ The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete.
This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes
This means that after the study is closed at UVa:

- *You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval*
- *You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)*
- *You cannot share your research data with another researcher outside of your study team without additional IRB approval*
- *Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.*

TABLE A: HIPAA Identifiers (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. Any other unique identifying number, characteristic, code that is derived from or related to information

about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)

APPENDIX: Sponsor

Sponsor Information

1. **Explain the sponsorship for this study.**

INSTRUCTIONS:
- List names of companies, institutes, foundations with which you have a grant or a contract from an entity that is not a support source.
- Example: This study is funded via a contract with the University of New York, which has a grant from the NIH to conduct this study. We will be receiving free drug from Glaxo. Glaxo will receive data prior to publication.
- If the outside entity will be monitoring the study or receiving data prior to publication enter them as a sponsor.
- If you are receiving things such as free supplies/ drug/ devices from a company who WILL NOT be monitoring the study or be receiving data prior to publication do NOT enter them here- enter this information under Support Source below.

Answer/Response: University of Virginia Department of Nephrology – Nephrology Clinical Research Center

2. **Do you confirm that you will obtain a contract/ material transfer agreement with the sponsor via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**?**

INSTRUCTIONS:
You should have answered YES to the following question in Protocol Builder:
--"Do you/will you have a contract with an outside entity to support this protocol?"

Answer/Response: N/A - departmental sponsor

APPENDIX: Support Source

The support source is any source outside of UVA providing support such as supplies/drug/device's. Do not enter a company/ organization as a supply source unless the support has been secured. The IRB-HSR must be notified and the consent form revised if a support source changes. (Example-the NIH or an investigator-initiated study in which the pharmaceutical company is providing drug free of charge.)

1. **Describe what will be provided and by whom**.
This study is an investigator initiated study that will be funded by Astra Zeneca. They will also be supplying study medication and placebo. Astra Zeneca will not be monitoring this study.

2. **Do you confirm that you will obtain a contract/ material transfer agreement with the provider via the Medical Center Procurement office or Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**? yes**

You should have answered YES to the following question in Protocol Builder:
Do you/will you have a contract with an outside entity to support this protocol?

Go through Medical Center Procurement if the item will be used on a patient in the Medical Center. Go through OSP is the item will be used outside of the Medical Center.

3. Will the Support Source be obtaining data prior to publication or performing monitoring of the study?

Astra Zeneca will not see the data prior to publication

APPENDIX: Transfer of Data Outside of UVa

1. What identifiers will be sent with the data?-NONE

YES	NO	1. Name
YES	NO	2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
YES	NO	3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*
YES	NO	4. Telephone numbers
YES	NO	5. Fax numbers
YES	NO	6. Electronic mail addresses
YES	NO	7. Social Security number
YES	NO	8. Medical Record number
YES	NO	9. Health plan beneficiary numbers
YES	NO	10. Account numbers
YES	NO	11. Certificate/license numbers
YES	NO	12. Vehicle identifiers and serial numbers, including license plate numbers
YES	NO	13. Device identifiers and serial numbers
YES	NO	14. Web Universal Resource Locators (URLs)
YES	NO	15. Internet Protocol (IP) address numbers
YES	NO	16. Biometric identifiers, including finger and voice prints
YES	NO	17. Full face photographic images and any comparable images
YES	NO	18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)
YES	NO	19. Any other information that could be used alone or in combination with other information to identify an individual. (*e.g. rare disease, study team or company has access to the health information and a HIPAA identifier or the key to the code* .)

2. How will data be sent?

____ Paper forms via mail/ FedEx, UPS etc.

__X_ Email: *Not allowed if you have answered YES to any item above.*

____FAX: *Not allowed unless receiving fax machine is in a restricted-access location, the intended recipient is clearly indicated, and that recipient has been alerted to the pending transmission and is available to pick it up immediately. Also verify FAX numbers before faxing and use FAX cover sheet with a confidentiality statement.*

____ **Devices such as flashdrive/ CD etc.:**
Not allowed if you have answered YES to any item above.

____ **Web Based Data Entry (e.g website, database, registry): Not Encrypted and Password Protected;** *Not allowed if you have answered YES to any item above.*

____ **Web Based Data Entry (e.g website, database, registry): Encrypted and Password Protected;**
If checked, do you confirm that you have verified with host site that data will be sent and stored in an encrypted fashion (e.g. via Secure FX, Secure FTP, HTTPS, PGP)? YES NO