Cover sheet

Date: 10/07/2021

NCT03520569

Protocol: IRB-HSR # 11948

Title: Effect of hyperglycemia on microvascular perfusion in healthy adults

Nov 16 2017

IRB-HSR PROTOCOL

Brief Summary/Abstract

We will study 22 healthy subjects (18-35yrs) four times as follows: 1) Saline + Octreotide + euglycemia; 2) Octreotide+ hyperglycemia; 3) Octreotide + hyperglycemia + insulin clamp and 4) Octreotide + Euglycemia + insulin clamp. The sequence of admissions will be assigned randomly. We will assess function in conduit (pulse wave velocity-PWV, augmentation index-AI and flow-mediated dilation-FMD), resistance (post-ischemic flow velocity-PIFV) and heart and skeletal muscle microvascular (contrast enhanced ultrasound-CEU) vessels.

This work will: a) identify whether vascular stiffness and indices of NO action are impaired throughout the arterial tree with hyperglycemia.

While multiple endpoints are measured in the proposed studies, we designate one primary macrovascular endpoint (flow mediated dilation) and one primary microvascular endpoint (microvascular blood volume); the studies are powered on these measures. We believe that our laboratories are in a unique position with respect to our demonstrated scientific expertise to deliver this fundamental information.

Background

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

The microvasculature is particularly susceptible to chronic hyperglycemic injury as manifest by known diabetes complications. For individuals with pre-diabetes and diabetes, acute hyperglycemic episodes exceed in frequency, duration and magnitude the glycemic fluctuations in healthy persons and increase in frequency during biological or psychological stress. Extensive *in vitro* studies show that vascular endothelial cells (EC) perceive hyperglycemia as an oxidative stress and respond by activating signaling pathways (e.g. protein kinase C), by increasing production of advanced glycation end products (e.g. methylglyoxal), by altered protein glycation via the GFAT pathway and have a more oxidized cytosolic compartment.

In humans acute hyperglycemia enhances plasma markers of EC stress (e.g. sICAM increased during a 2 hr hyperglycemic clamp) and simultaneously giving insulin blunted this response in both healthy and DM2 subjects (26) Perkins et al (9), using the pancreatic clamp technique, reported that 4 hrs of hyperglycemia increased inflammatory markers (plasma VCAM, ICAM, p- and e-selectin, PAI-1 and IL-6) in obese humans. Interestingly, plasma concentrations of these markers fell if plasma insulin was increased to high physiologic levels during hyperglycemia, implicating a regulatory role for insulin. The endothelial source for these biomarkers (macro-or micro vasculature or both) is not known. Brachial artery endothelial function measured as FMD (another "marker" of vascular health) was suppressed by hyperglycemia with basal insulin and giving insulin prevents this inhibition (9). These and other studies assessing circulating biomarkers of EC origin or FMD suggest that acute

hyperglycemia has a deleterious vascular effect. However, these indices do not directly measure macrovascular flow or microvascular perfusion, vital issues for the tissues per se. A very few human studies have assessed hyperglycemia's effects on microvascular perfusion. In the eye acute hyperglycemia increased retinal flow (measured by videomicroscopy) (12, 13). By contrast, in skin hyperglycemia decreased flow (measured by laser-Doppler flowmetry) (Cuypers, 2000 #6750). Brain perfusion has been measured by arterial spin-labeling MRI in rats (but not in humans) and declined with overnight hyperglycemia with suppressed insulin (27). None of these studies addressed the interaction between insulin or insulin resistance and perfusion and none involved skeletal or heart muscle. CEU provides a noninvasive method to measure two components of microvascular perfusion i.e. microvascular blood volume (MBV) and microvascular flow velocity (MFV). The product of these variables is a measure of microvascular perfusion (28). Our laboratory has extensive experience using CEU to measure perfusion in human cardiac and skeletal muscle. We have previously reported that insulin, exercise, GLP-1, mixed meal ingestion, and angiotensin II each enhance skeletal muscle microvascular perfusion by recruiting under perfused capillaries and increasing MBV (15, 16, and 29). We have also shown that insulin's effect to recruit skeletal muscle microvasculature is lost in insulin resistant subjects with metabolic syndrome, obesity, or when otherwise healthy subjects are rendered insulin resistant by lipid infusion. We have also shown that in healthy volunteers insulin and GLP-1 can each increase MBV in human myocardium. Raising plasma free fatty acid concentrations blunts the effect of insulin on the myocardium as well as on skeletal muscle (25, 29). In these studies of either skeletal or cardiac muscle, MFV was not significantly changed. In a similar vein, an early study using CEU reported that meal ingestion in individuals with type 2 diabetes decreased MBV without affecting MFV (30). As noted earlier, meal ingestion is a more complex stimulus than hyperglycemia per se. A recent CEU study used the pancreatic clamp to provoke hypoinsulinemic hyperglycemia (~220 mg/dl) and reported a decreased myocardial blood flow reserve (provoked by an adenosine agonist) in healthy volunteers (31). No measure was obtained of the direct effect of hyperglycemia. Interestingly, the inhibitory effect of hyperglycemia was attributed to changes in MFV without any significant effect on MBV. The study did not test whether the octreotide (used in the pancreatic clamp) per se affected microvascular responses. Given the scant available data regarding the effect of hyperglycemia on microvascular perfusion in either skeletal or cardiac muscle we propose to establish the vascular impact of acute hyperglycemia in the clinical setting in normal healthy controls.

Motivation for studying the effects of acute hyperglycemia on microvascular function in healthy individuals comes from: a) the extensive data showing deleterious effects of acute hyperglycemia on endothelial cell biology; b) epidemiologic data indicating a significant relationship between post prandial hyperglycemia and CVD events; and c) observational data indicating that stress hyperglycemia during acute coronary syndrome predicts poor clinical outcomes.

We have extensive experience with each of the 5 methods proposed to assess vascular function. These include using ultrasound (Philips Epic 7) for CEU, PIFV and FMD and aplanation tonometry (SphygmoCor, AtCor Medical) for PWV and AI measurements. We also have

experience with assays of circulating insulin, FFA, inflammatory cytokines (hsCRP, VCAM, ICAM, IL6) and measurement of nitric oxide (Sievers NO analyzer) in plasma.

Hypothesis to be tested

Building on extensive experience, we hypothesize a) that in healthy controls acute hyperglycemia per se will rapidly (within 3 hrs) inhibit both heart and skeletal muscle microvascular perfusion; b) that hyperinsulinemia will prevent hyperglycemia's adverse effect on heart and skeletal muscle microvascular perfusion in healthy insulin-sensitive subjects.

Study Design: Biomedical

1. Will controls be used?
Answer/Response: Yes

► IF YES, explain the kind of controls to be used.
Answer/Response: Each subject will serve as his/her own control.

2. What is the study design?
Answer/Response:
Not blinded. Subject will complete 4 arms in a randomized fashion

3. Does the study involve a placebo?
Answer/Response: No

► IF YES, provide a justification for the use of a placebo
Answer/Response:

Human Participants

Ages: __18-35__
Sex: __M and F__
Race: __All_

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol.
Answer/Response: 22

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.
Answer/Response:
We need 22 lean adults in order to have a two-sided hypothesis test that has at least 80% power and a type I error rate of 0.05 to test our primary hypothesis. Please see the biostatistical section for a more complete explanation of what we expect to see and why. Each subject will have 4 admissions (thus serving as his/her own control) as

follows: Saline + Octreotide + Euglycemia; Octreotide + Hyperglycemia; Octreotide + Hyperglycemia + insulin clamp; Octreotide + Euglycemia + insulin clamp. Based on our experience, we will have a number of drop outs due to screen fails, subjects changing their mind after signing consent form, some subjects will not finish entire protocol and some will have inadequate imaging. Accordingly, we are planning to recruit 50 subjects in order to complete the necessary 22 subjects needed for statistical analysis.

3. **How many subjects will be enrolled at all sites?**
   Answer/Response: 50

4. **How many subjects will sign a consent form under this UVa protocol?**
   Answer/Response: 50

5. **Provide an estimated time line for the study.**
   Answer/Response:
   100% will be enrolled in two years, and completion of data will be 3 years.

Inclusion/Exclusion Criteria

1. **List the criteria for inclusion**

Answer/Response:

- Healthy with no chronic illness
- Age 18-35
- Normal BMI (18-25)
- Normal screening labs or no clinically significant values

2. **List the criteria for exclusion**

Answer/Response:

- First degree relative with Type 2 Diabetes
- Smoking presently or in the past 6 months
- Medications that affect the vasculature
- Overweight or other indications of insulin resistance
- Elevated LDL cholesterol > 160
- Elevated BP > 140/90
- History of congestive heart failure, ischemic heart disease, severe pulmonary disease, liver or kidney disease, bleeding disorders
- Any vascular disease such as myocardial infarction, stroke, peripheral vascular disease
- Presence of an intracardiac or intrapulmonary shunt (we will screen for this by auscultation during the physical exam by PI).
- Pregnant or breastfeeding.
- Known hypersensitivity to perflutren (contained in Definity)

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

Answer/Response:
May not be taking any medications that affect the vasculature, either by dilatation of the vessels, or increase or decrease in the blood flow.

Statistical Considerations

1. Is stratification/randomization involved?

Answer/Response: Yes

►IF YES, describe the stratification/ randomization scheme.

Answer/Response:
Each subject will be admitted four times. The type or order of admission is randomized using a randomization table and admissions will be approximately 2-4 weeks apart. The randomization will not be blinded.

►IF YES, who will generate the randomization scheme?

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
_____ UVa Investigational Drug Service (IDS)
___X__ Other: Specify Answer/Response:
Randomization table obtained from online source-copy included

2. What are the statistical considerations for the protocol?

By design, each of the above protocols affords a paired comparison of the changes which occur between measurements obtained at baseline and at the end of the infusion protocol. Principal endpoints are the changes in microvascular perfusion in both skeletal and cardiac.
Referring to Fig 1 for protocol A this comparison will indicate whether 3 ½ hours of octreotide infusion with basal insulin replacement and maintenance of euglycemia per se influences microvascular perfusion in either tissue. As noted above, if octreotide has no specific effect on the primary microvascular endpoint (MBV) then in protocols B, C, and D, we believe paired comparison of baseline and end of study variables will be justified.
This may prove advantageous as it may minimize the effect of day-to-day or week to week variations in responses resulting from uncontrolled variables (diet, exercise, emotional stress etc.) For protocol B this comparison will address whether hyperglycemia for 3 ½ hours in the setting of octreotide infusion, and basal insulin replacement affects microvascular perfusion. Combined protocols A and B analyzed using a 2-way ANOVA will allow analysis of whether time or treatment differences exist and will delineate the effect of hyperglycemia per se on skeletal and cardiac muscle microvascular perfusion, independent of any effect of octreotide per se. In protocols C and D introduce hyperinsulinemia as additional variable under either hyperglycemic or euglycemic conditions with octreotide infusion persisting throughout. Comparing the baseline measurements (C-1) to those obtained at the end of the study (C-2) addresses whether insulin affects microvascular perfusion in the setting of hyperglycemia. Comparison of the

changes of indices of microvascular perfusion between protocol C and D (2-way ANOVA) will provide a measure of whether acute hyperglycemia induces resistance to insulin's action to enhance cardiac and skeletal muscle microvascular perfusion. A number of other comparisons can be made from the four infusion protocols. Thus, comparing measures at D1 and A2 will allow assessment of the reproducibility of measures of microvascular function following three and half hours of octreotide with basal insulin replacement and euglycemia).
For macrovascular function we will use FMD as the primary endpoint for macrovascular endothelial function and PWV as the primary endpoint for measures of central aortic stiffness. This was selected because we know from prior experiments that physiologic hyperinsulinemia in healthy subjects enhances FMD. While it is difficult to power all endpoints of the study at this point in time, we note that our published studies have examined vascular insulin action in cohorts of 12-18 subjects and we have found that 12-14 subjects are sufficient to detect a 30% difference in microvascular function in response to insulin. Thus, with 20 subjects per group, and with at least 16 subjects completing all four studies we expect to have at least an 80% power of detecting a 30% between-group mean difference in each endpoint.
It will be particularly interesting if the myocardial microvasculature does not respond to insulin by enhanced microvascular perfusion during the hyperglycemic clamp (protocol C) as we have found in healthy adults (25). To our knowledge there is no available information on hyperglycemia's effect on baseline or insulin responsive myocardial microvasculature. Given that acute "stress" hyperglycemia in the setting of acute coronary syndrome is such a strong predictor of mortality (1) defining a mechanism which might contribute to this microvascular dysfunction would be significant.

3. Provide a justification for the sample size used in this protocol.
See above

4. What is your plan for primary variable analysis?
See above

5. What is your plan for secondary variable analysis?
The secondary variables include PWV, AI, PIFV, oxygen saturation of skeletal muscle (NIRS), blood pressure, heart rate, as well as plasma insulin, free fatty acid and blood glucose concentration. These variables will be compared within each admission and across all four admissions using repeated measures ANOVA.

6. Have you been working with a statistician in designing this protocol?
Answer/Response: No

IF YES, what is their name?
Answer/Response:

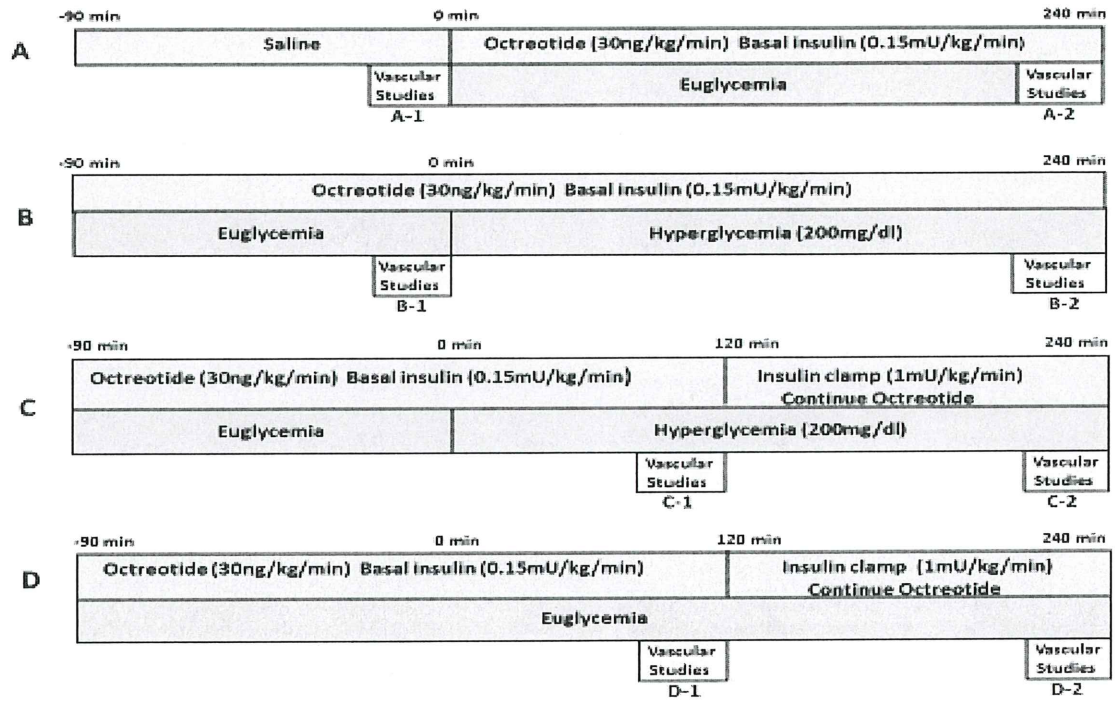
7. Will data from multiple sites be combined during analysis?
Answer/Response: No

Biomedical Research

1. What will be done in this protocol?

Screening visit
On the first day, the subject will fast overnight and come to the CRU the next morning. The consent form will be signed. Vital Signs, height and weight will be obtained. Pulse oximetry will be done to measure the percentage of oxygen in the blood. If the result is <90% subject will not be allowed to participate. Blood will be drawn for complete blood count, lipid profile, fasting glucose, comprehensive metabolic, and if female, a pregnancy test (15cc of blood). A history and brief physical examination will be obtained. Total time commitment for this visit is approximately 1 hour.

If all screening parameters are normal or not clinically significant, we will schedule four admissions: 1) Saline + Octreotide + euglycemia; 2) Octreotide+ hyperglycemia; 3) Octreotide + hyperglycemia + insulin clamp and 4) Octreotide + Euglycemia + insulin clamp. The sequence of admissions will be assigned randomly and will be approximately 2 to 4 weeks apart.



Measurements that will be performed at all admissions

- **Augmentation Index (AI)** This measures the pulse wave of the vessel and its characteristics which is an assessment of the stiffness of the aorta. We will use an aplanation tonometer from SphygmoCor. This is done by placing the probe, which looks like a "fat" pen, over the radial artery at the wrist and measuring several waveforms. This will take 2-5 minutes.
- **Pulse Wave Velocity (PWV)** This measures the time difference between the pulse wave at the carotid artery and the pulse wave at the femoral artery. This will allow us to assess the "stiffness" of the larger vessels. The shorter the time difference, the stiffer or less elastic the vessels are. We will use the same device as described above. The subject is attached to an ECG and the probe is placed over the carotid artery in the neck. We measure the time between the heartbeat (as seen on the ECG) and when the probe picks up the pulse wave with the tonometer. We will repeat the process at the femoral artery in the groin area. Finally we will look at the distance between the two vessels as well as the time difference. This will take about 5-10 minutes.
- **Flow mediated Dilation (FMD)** Brachial artery diameter is measured using ultrasound at baseline and then after five minutes of forearm ischemia. The subject will be placed supine in bed. The first measurement is taken (velocity and diameter) and then a blood pressure cuff will be placed around the forearm and pumped to 200 mm/Hg and held for 5 minutes. The brachial artery on the same arm will be observed with ultrasound as the BP cuff is deflated and for 3 minutes post cuff deflation. This will take approximately 10 minutes.

- **Contrast enhanced ultrasound (CEU)** This is used to look at cardiac and skeletal muscle microvasculature using microbubbles as a measure of red blood cell flow. Lipid coated, perflurocarbon filled microbubbles (brand name is Definity) are approved by the FDA for imaging of the microvasculature in cardiac muscle. In this study they are used in an experimental manner because we are looking at skeletal muscle in addition to heart; however the method of administration (these microbubbles are given as a systemic infusion) and dose (maximum 1.5ml per day) is exactly the same as used for the heart. We are simply moving the ultrasound probe from the chest to the forearm muscle. We will use a mechanical index of 0.8 for the heart and 1.5 for the skeletal muscle. We have used this technique to look at skeletal muscle for over 16 years. This will take approximately 10 minutes.
- **Near infrared spectroscopy (NIRS)** This is used to look at hemoglobin content (both oxygenated and deoxygenated) and oxygen saturation in the muscle. A small square fiber optic sensor (2 x 4 inches) will be placed on the skin over the forearm muscle. . Light is emitted and as it travels through the different tissue in the arm (bone, fat, muscle, blood etc) it will create a mathematical measurement that has to do with density on the attached computer. The measurement takes 3-5 min.

A. <u>Saline + Octreotide + Euglycemia (~10 hours)</u>

On the day of admission, the subject will be admitted to the CRU at ~ 7:00AM. The subjects will have been asked to fast after 10PM the evening before. Female subjects will have a urine pregnancy test. We will insert 2 peripheral IV lines. One will be in an antecubital vein and this will be used for infusion of saline, octreotide, insulin, glucose and microbubbles. The second will be placed in the lower forearm of the same arm and will be used for sampling. This will be kept patent with a normal saline infusion.
After resting for 1 hour we will begin the study as follows.

- Blood pressure, heart rate and oxygen saturation will be obtained. If the oxygen saturation <90% the subject will be excluded.
- Blood will be drawn (~10 cc) for samples of glucose, insulin, and inflammatory cytokines from the sampling IV.
- We will begin a saline infusion at 30ml/hr.
- This is considered time -90 min.

We will measure insulin every 30 minutes for duration of study (~18cc).

Between -30 and 0 minutes

- We will measure NIRS of forearm muscle
- Next we will measure PWV followed by AI
- Next we will measure FMD
- Next we will perform CEU of the heart and skeletal muscle
- Subjects will be placed on a continuous cardiac monitor for 30 minutes following the end of the microbubble infusion. There will always be a resuscitation cart as well as qualified personnel available should the need arise.

- We will repeat the blood sampling (~10cc) performed at time -90.
- We will begin an infusion of Octreotide (30ng/kg/min).
- We will begin an insulin infusion (dose is 0.15mU/kg body wt/min).
- We will also begin glucose infusion (20% variable rate) to maintain euglycemia.
- This is considered time 0 min.
- We will measure plasma blood glucose every 10 min through 240 min (~23cc blood).
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to maintain plasma glucose within 10% of the fasting concentration.

- We will repeat the entire sequence of vascular measurements between 210 and 240 minutes.
- We will also repeat blood draw for glucose, insulin and inflammatory cytokines (~10cc).
- At time 240 minutes the study is complete and the insulin and octreotide infusion will be stopped.
- Subject will be fed a meal.
- Blood glucose measurements will continue to be made at 10 minute intervals (~15 cc of blood) and the rate of the glucose infusion adjusted to maintain normal blood glucose levels. This will continue until blood glucose is within normal range without the need for the glucose infusion.
- We will also continue to test blood glucose every 15 minutes (~5cc blood) for one hour after glucose infusion stopped to be sure that blood glucose levels stay within normal range.

When the sampling for blood glucose is complete subjects will have all catheters removed and vital signs done. If stable they will be discharged.

Total blood taken for this admission is approximately ~91cc.

B. <u>Octreotide + Hyperglycemia admission (~10hrs)</u>

On the day of admission, the subject will be admitted to the CRU at ~ 7:00AM. The subjects will have been asked to fast after 10PM the evening before. Female subjects will have a urine pregnancy test. We will insert 2 peripheral IV lines. One will be in an antecubital vein and this will be used for infusion of octreotide, insulin, glucose and microbubbles. The second will be placed in the lower forearm of the same arm and will be used for sampling. This will be kept patent with a normal saline infusion.
After resting for 1 hour we will begin the study as follows.

- Blood pressure, heart rate and oxygen saturation will be obtained. If the oxygen saturation <90% the subject will be excluded.
- Blood will be drawn (~10cc) for samples of glucose, insulin, and inflammatory cytokines from the sampling IV.
- We will begin an infusion of Octreotide (30ng/kg/min).

- We will also begin the insulin infusion (dose is 0.15mU/kg body wt/min).
- We will also begin glucose infusion (20% at variable rate) to maintain euglycemia.
- This is considered time -90 min.
- We will draw blood every 10 min to measure blood glucose from time -90 min to 0 min (~12cc).
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to maintain plasma glucose within 10% of the fasting concentration

We will measure insulin every 30 minutes for duration of study (~18cc).

At time 0 minutes

- We will measure NIRS of forearm muscle
- Next we will measure PWV followed by AI
- Next we will measure FMD
- Next we will perform CEU of the heart and skeletal muscle
- Subjects will be placed on a continuous cardiac monitor for 30 minutes following the end of the microbubble infusion. There will always be a resuscitation cart as well as qualified personnel available should the need arise.
- We will repeat the blood sampling (~10cc) performed at time -90.
- Next we will adjust the glucose rate to achieve hyperglycemia (200mg/dl).
- We will measure plasma blood glucose every 5 minutes starting at time 0 min through 240 min (45cc blood).
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to raise and maintain plasma glucose concentration at 200mg/dl.

- We will repeat the entire sequence of vascular measurements between 210 and 240 minutes.
- We will also repeat blood draw for glucose, insulin and inflammatory cytokines (~10cc).
- At time 240 minutes the octreotide, insulin and glucose infusion will be stopped.
- Subject will be fed a meal.
- Blood glucose measurements will continue to be made at 10 min intervals (~ 15 cc of blood) until blood glucose is within normal range. We will continue to test blood glucose every 15 minutes (~5cc blood) for one hour to be sure that blood glucose levels stay within normal range.

When the sampling for blood glucose is complete subjects will have all catheters removed and vital signs done. If stable they will be discharged.

Total blood taken for this admission is approximately ~125cc.

C. Octreotide + Hyperglycemia + insulin clamp (~10 hours)

On the day of admission, the subject will be admitted to the CRU at ~ 7:00AM. The subjects will have been asked to fast after 10PM the evening before. Female subjects will have a urine pregnancy test. We will insert 2 peripheral IV lines. One will be in an antecubital vein and this will be used for infusion of octreotide, insulin, glucose and microbubbles. The second will be placed in the lower forearm of the same arm and will be used for sampling. This will be kept patent with a normal saline infusion.
After resting for 1 hour we will begin the study as follows.

- Blood pressure, heart rate and oxygen saturation will be obtained. If the oxygen saturation <90% the subject will be excluded.
- Blood will be drawn (~10 cc) for samples of glucose, insulin, and inflammatory cytokines from the sampling IV.
- We will begin an infusion of Octreotide (30ng/kg/min).
- We will also start the insulin infusion (dose is 0.15mU/kg body wt/min).
- We will also start glucose infusion (20% at variable rate) to maintain euglycemia.
- This is considered time -90 min
- We will draw blood every 10 min for glucose from time -90 min to 0 min (~12cc)
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to maintain plasma glucose within 10% of the fasting concentration
- .

We will measure insulin every 30 minutes for duration of study (~18cc).

At time 0 minutes

- We will repeat the blood sampling (~10cc) performed at time -90.
- We will adjust the glucose rate to achieve hyperglycemia (200mg/dl).
- We will measure plasma blood glucose every 5 minutes starting at time 0 minutes through 240 minutes (45cc blood).
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to raise and maintain plasma glucose concentration at 200mg/dl.

Between 90-120 min we will conduct the following:

- We will measure NIRS of forearm muscle
- Next we will measure PWV followed by AI
- Next we will measure FMD
- Next we will perform CEU of the heart and skeletal muscle
- Subjects will be placed on a continuous cardiac monitor for 30 minutes following the end of the microbubble infusion. There will always be a resuscitation cart as well as qualified personnel available should the need arise.

- We will repeat the blood sampling (~10cc) performed at time -90. At time 120 min, we will increase the insulin infusion (dose is 1mU/kg body wt/min).

- We will repeat the entire sequence of vascular measurements between 210 and 240 min
- We will also repeat blood draw for glucose, insulin and inflammatory cytokines (10cc).
- At time 240 minutes the clamp is complete and the insulin and octreotide infusion will be stopped.
- Subject will be fed a meal.
- Blood glucose measurements will continue to be made at 10 minute intervals (~15 cc of blood) and the rate of the glucose infusion adjusted to maintain normal blood glucose levels. This will continue until blood glucose is within normal range without the need for the glucose infusion.
- We will also continue to test blood glucose every 15 minutes (~5cc blood) for one hour after glucose infusion stopped to be sure that blood glucose levels stay within normal range.

When the sampling for blood glucose is complete subjects will have all catheters removed and vital signs done. If stable they will be discharged.

Total blood taken for this admission is approximately ~125cc.

D. <u>Octreotide + Euglycemia + insulin clamp (~10 hours)</u>

On the day of admission, the subject will be admitted to the CRU at ~ 7:00AM. The subjects will have been asked to fast after 10PM the evening before. Female subjects will have a urine pregnancy test. We will insert 2 peripheral IV lines. One will be in an antecubital vein and this will be used for infusion of octreotide, insulin, glucose and microbubbles. The second will be placed in the lower forearm of the same arm and will be used for sampling. This will be kept patent with a normal saline infusion.
After resting for 1 hour we will begin the study as follows.

- Blood pressure, heart rate and oxygen saturation will be obtained. If the oxygen saturation <90% the subject will be excluded.
- Blood will be drawn (~10 cc) for samples of glucose, insulin, and inflammatory cytokines from the sampling IV.
- We will begin an infusion of Octreotide (30ng/kg/min).
- We will also start the insulin infusion (dose is 0.15mU/kg body wt/min).
- We will also start glucose infusion (20% at variable rate) to maintain euglycemia.
- This is considered time -90 min.
- We will draw blood every 10 min for glucose from time -90 min to 120 min (~22cc).

- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to maintain plasma glucose within 10% of the fasting concentration

We will measure insulin every 30 minutes for duration of study (~18cc).

At time 0 we do not do anything but continue above infusions.

Between 90-120 min we will conduct the following:

- We will measure NIRS of forearm muscle
- Next we will measure PWV followed by AI
- Next we will measure FMD
- Next we will perform CEU of the heart and skeletal muscle
- Subjects will be placed on a continuous cardiac monitor for 30 minutes following the end of the microbubble infusion. There will always be a resuscitation cart as well as qualified personnel available should the need arise.
- We will repeat the blood sampling (~10cc) performed at time -90. Upon completion we will begin the insulin clamp as follows:

- We will increase the insulin infusion (dose is 1mU//kg body wt/min)
- This is time 120 minutes
- We will measure plasma blood glucose every 5 minutes starting at time 120 minutes through 240 minutes (~21cc blood).
- The values for blood glucose are measured immediately and used to adjust the rate of infusion of a glucose solution (20% dextrose) in order to maintain plasma glucose within 10% of the fasting concentration

- We will repeat the entire sequence of measurements between 210 and 240 minutes.
- We will also repeat blood draw for glucose, insulin and inflammatory cytokines (~10cc).
- At time 240 minutes the clamp is complete and the insulin and octreotide infusion will be stopped.
- Subject will be fed a meal.
- Blood glucose measurements will continue to be made at 10 minute intervals (~15 cc of blood) and the rate of the glucose infusion adjusted to maintain normal blood glucose levels. This will continue until blood glucose is within normal range without the need for the glucose infusion.
- We will also continue to test blood glucose every 15 minutes (~5cc blood) for one hour after glucose infusion stopped to be sure that blood glucose levels stay within normal range.

When the sampling for blood glucose is complete subjects will have all catheters removed and vital signs done. If stable they will be discharged.

Total blood taken for this admission is approximately ~111cc.

Total blood taken for entire study is ~ 467cc

1. Lipid Profile
2. Complete Blood count
3. Blood chemistries
4. Glucose
5. Insulin
6. Inflammatory cytokines
7. Pregnancy (in females), blood for screening and urine at each admission.

2. List the procedures, in bullet form, that will be done for <u>RESEARCH PURPOSES</u> as stipulated in this protocol.
Answer/Response: ALL

3. Do you confirm that, except for blood draws through a peripheral site, that all invasive procedures will be performed by a licensed health care provider under the supervision of an MD?
Answer/Response: Yes

4. 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?
Answer/Response: No

5. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? This includes ALL procedures, assessments and evaluations that are being done for <u>RESEARCH PURPOSES</u> that may or may not be considered investigational.

Answer/Response: 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.

____This examination(s) utilizes non-standard/investigational, technique, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

6. Do any of the procedures listed above, under question # 2, utilize any imaging procedures for RESEARCH PURPOSES?

Examples: ultrasound, CT scans/ x-rays etc.

Answer/Response: yes

IF YES, list procedures:

Answer/Response: Ultrasound

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

__**X**__This imaging research examination utilizes the same imaging techniques, equipment, scanning sequences that would be used if the subject were to have the imaging performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

►If checked, answer the following:

Will the images be read by a licensed radiologist and the reading placed in the subject's medical record?

Answer/Response: No

►IF NO: The PI takes full responsibility for the identification of incidental findings:

- The PI will have all incidental findings reviewed by a radiologist who will advise the PI regarding clinical significance.
- 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.

_____This imaging research examination utilizes non-standard/investigational imaging modality, techniques, equipment, scanning sequences, etc. It is impossible to determine the significance of such images, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

9 Are any aspects of the study kept secret from the participants?

Answer/Response: No

▶ **IF YES, describe:**

Answer/Response:

10. Is any deception used in the study?

Answer/Response: No

▶ **IF YES, describe:**

INSTRUCTIONS: Describe the deception involved and the debrief procedures. Attach a post-experiment debriefing statement and consent form offering participants the option of having data destroyed.

Answer/Response:

11. If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.

Example: If the subject will be taking an investigational drug, will they need to be put back on an approved drug when they have completed the study? If yes, explain how this will be accomplished and who will cover the cost. If the subject has a device implanted will it be removed? Again- who will cover the cost of the removal?
Instructions: Answer NA if this study does not involve a study treatment.

Answer/Response: NA

12. Will your study involve measures (C-SSRS/BID/SCID etc.) used to assess for depression and/or suicidality <u>for research purposes?</u> ___No

Answer this question YES if any of the following apply:

13. **Where will the study procedures be done?**

Check One:

UVA medical center facilities (In patient or outpatient)

___x_ UVa , but not medical center facilities: LIST specific location Answer/Response:

Clinical Research Unit (CRU)

____ Other LIST specific location Answer/Response:

14. If the study involves medical risk and study procedures will be done outside of the UVa Medical Center what is your plan to protect the subjects in case of a medical emergency?

Check all applicable options:

___x __ MD, RN, onsite during procedures
_____ Individual trained in CPR on site during procedures
_____ AED and Individual trained to use it onsite
_____ Call 911
_____ Other : Describe Answer/Response:

Unapproved Device Use
(Unapproved Device being used but not evaluated)

INSTRUCTIONS: This section is to provide the IRB with information about the safety of a device that is being USED, but not evaluated in this study for safety and efficacy. The device may have FDA approval and is being used for a non-approved indication OR the device may not have FDA approval [these are typically known as Research Use Only (RUO) Devices]. Again the RUO Device is only being USED and NOT being evaluated for safety and efficacy in this study. The information below will be used by the IRB to make a minimal risk determination regarding this protocol.

1. **List name of device(s) being used in an unapproved manner in this protocol.**

Per the statute: Federal Food, Drug, and Cosmetic Act Sec 201.h [21USC321]
DEVICE: (h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Answer/Response:
Harvard infusion pump
Oxiplex TS (near infrared spectroscopy)

2. **Do you confirm the device is only being USED and NOT being evaluated in this study?**

Answer/Response: Yes

3. **Is the device a Research Use Only (RUO) device?**

IF YES, submit the manufactures brochure/information regarding the RUO with other documents at the time of pre-review. IMPORTANT: The RUO designation is made by the FDA. The package insert MUST stipulate that this is a RUO device.

Answer/Response:

Only the Oxiplex TS-FDA confirmation on file

► If the device is a RUO device, do you agree to use the device according to instructions in the manufacturers brochure?

Answer/Response: Yes

► If the device is NOT a RUO device, is the device currently approved for any indication?

Answer/Response:

No for Harvard pump

► If the device is currently approved list the indication:

INSTRUCTIONS: Also submit the Manufacturer's Brochure

Answer/Response:

► If the device is currently approved, do you confirm that results will not be used in clinical care of the subject (e.g. will not be used for diagnosis or treatment?)

Answer/Response:

4. **In how many humans has this device been used previously as it is being used in this study?**

Answer/Response:

Harvard Pump: We have used this device in this manner for 24 years at UVA and have done 2000+ studies

Oxiplex TS-unknown

5. **Describe pertinent human data that is available regarding the safety of this device as you are using it in this protocol.**

Answer/Response:

Harvard pump-N/A

Oxiplex TS-unknown

6. **If this protocol will be used in children, describe any previous use of this device with children of a similar age range as it is being used in this study.**

Answer/Response: N/A

7. **What steps will be taken to minimize risk?**
   Answer/Response: Qualified personnel will always be at the beside when either of these devices are used

8. **Would you consider the use of this device to be minimal risk? Why or why not?**

Minimal Risk: probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 45CFR46.102

   Answer/Response:
   Harvard pump--Minimal risk as this is just used for relatively short infusions and study team present and monitoring at all times.
   Oxiplex TS-Minimal risks as non-invasive measurement that takes a few minutes.

Drug Information

1 **What is the drug name, manufacturer and IND# if available?**
   Answer/Response:

Drug name	Drug Source	IND#
Octreotide	Novartis	N/A
Insulin	Novo Nordisk	N/A
Definity Microbubbles	Lantheus Medical Imaging	N/A
Dextrose 20%	Hospira	N/A

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?
   Answer/Response: N/A

3. What is the phase or stage of this study?
   e.g. Phase 1,2 or 3, pivotal, pilot, post-marketing
   Answer/Response: N/A

Pharmacy-Investigational Drugs/Biologics

1. **What is the name of the investigational drug/biologic?**
   Answer/Response:
   Regular insulin
   Octreotide
   Definity
   Dextrose 20%

2. Where will the subjects be seen for the administration/dispensing of the drug?

_____ Inpatient Unit: Specify Answer/Response:

___X__ Outpatient Unit: Specify Answer/Response: Clinical Research Unit

3. What dose will be utilized in this study?

Answer/Response:
Regular insulin-1mU/kg/minute IV on clamp days otherwise low rate of 0.15mU/kg/min).
Definity-1 vial per study day
Octreotide – 30ng/kg/min

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

Answer/Response:
Regular insulin-varying times (depending on study) low dose same schedule as Octreotide except during insulin clamp which is a higher dose. Please see protocol figure provided.
Definity-1 vial per study day
Octreotide – varying times depending on study- please see protocol figure 1 provided.
Dextrose 20%-entire 5 hrs (at variable rate) for each admit except visit A-see figure 1.

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

Answer/Response:
As noted above

6. What route of administration will be utilized?

Answer/Response:
Regular insulin-IV
Definity-IV
Octreotide-IV
Dextrose 20 %- IV

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

___x__ YES (Octreotide) D20 dispensed
___x__ NO- Drug will be prepared and/or administered per package insert

The insulin will be mixed in normal saline and 2 ml of subjects own blood on study day.

▶ IF YES, complete the following information under 7a-7d.
If you need assistance completing this section contact the Investigational Pharmacists at 982-1048

7a. Concentration

_____ Standard
__x___ Non- Standard-Specify Answer/Response: Octreotide- The dose is 30ng/kg/min-4 admits are 5 hr infusions and Admit A is 3.5-see fig 1

7b. Diluents

_____ Standard
___x__ Non- Standard-Specify Answer/Response: Octreotide to be mixed with normal saline.

7c. Stability after prepared
___x__ Standard
Non- Standard-Specify Answer/Response

7d. Special storage requirements
___x__ Standard
_____ Non- Standard-Specify Answer/Response:

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?
Answer/Response: No

▶ IF YES, provide specifics
Answer/Response:

9. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.?
Answer/Response: No

▶ IF YES, provide specifics
Answer/Response:

10. How will missed doses be handled?
Answer/Response: N/A

11. Will a comparator (active or placebo) be utilized in the protocol?
Answer/Response: No

▶ IF YES, comparator is:
_____ Active FDA approved drug: Provide name and dose of drug: Answer/Response:

_____ Placebo: Describe: Answer/Response:

12. Does this study involve research on a drug, biologic, supplement or food additive?
Answer/Response: Yes

▶ IF YES, is this study investigator initiated?
Answer/Response: Yes

IF YES, answer questions # 13 and 14
IF NO, answer question # 13 only.

13 Are you using a drug/supplement/ food additive in a manner not approved by the FDA?
Answer/Response: Yes
Insulin for euglycemia clamp is used to look at insulin sensitivity. This drug has been used in this manner for 60+ years.
Definity is used in the same manner for both heart (FDA approved) and skeletal muscle, we are just moving the probe to the arm after looking at the heart
Octreotide has been approved for patient use since 1988. We are using it to decrease endogenous insulin, glucagon and GH secretion during clamp.

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.
Answer/Response: Please see attached package insert for all drugs

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.
Answer/Response: Please see attached package insert for all drugs

13c. Have there been any human deaths associated with this drug?
Answer/Response: Please see attached package insert for all drugs

13d. In how many humans has this drug been used previously?
Answer/Response: Please see attached package insert for all drugs

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.
Answer/Response: N/A

14. Do the following criteria apply? NO 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;

_____ 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.

If Not checked- explain why you believe the risk to subjects is not increased:

Answer/Response:

- Dr. Eugene Barrett has extensive research experience administering insulin to look at insulin sensitivity in the normal and diabetic population. Insulin has been safely used in this manner for over 60 years. Procedures are in place to minimize the risk to subjects such as q 5 min blood glucose monitoring during the insulin clamp procedure.
- Although the Definity is approved for imaging cardiac instead of skeletal muscle, we are using the same dose and route of administration. We are imaging cardiac and skeletal muscle in this study.
- Octreotide has been approved for patient use for a variety of reasons since 1988. We are using it to decrease endogenous insulin secretion during the insulin clamp. It has also been used in this way for research for many years.

__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?
Answer/Response: No

► IF YES is the study required to be done by the FDA?
Answer/Response: No

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**
   (e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
   Answer/Response:
   There is nothing in between visits to monitor. Everything is done/infused on the study days.
2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
   (e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
   Answer/Response: N/A

Specimens

Specimen Information

1. Describe the type of specimen to be used:
Answer/Response:
Urine and Blood

2. Will the specimen be obtained BEFORE a subject has signed a consent form?
Answer/Response: No

3. Will you be using discarded specimens?
Answer/Response: No

►IF YES, do you confirm that it will be obtained either from pathology, a clinical lab or the UVA Biorepository & Tissue Research Facility (BTRF)?
Answer/Response:

►IF you will not obtain the specimen from the sources listed above, describe the process for obtaining the discarded tissue.
Answer/Response:

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

►IF NO, where will blood be drawn? *Check all that apply*

_____in clinical labs
__X___ in the clinical research unit (CRU)
_____ in a clinical setting
_____ in a research lab which has an IBC#
_____ Other: Explain Answer/Response:

►IF NO, who will draw the blood?

_____ a member of the study team who is an individual licensed to practice medicine or osteopathy, a nurse practitioner, or a physician assistant employed by UVa School of Medicine

_____x_a member of the study team who is a person trained to draw blood by an individual licensed to practice medicine or osteopathy, a nurse practitioner, or a physician assistant employed by UVa. *Written documentation of training will be kept in research files. Individual also has current training in handling of blood borne pathogens*

►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.

__X___ healthy, non-pregnant adults who weigh at least 110 pounds.

___X__ Amount will NOT exceed 550 cc in an 8 week period

_____ Amount to exceed 550 cc in an 8 week period

_____ Non- healthy or pregnant adults and/or children

_____ 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

►IF NO, will blood ONLY be obtained via a peripheral blood stick?
Answer/Response: No

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?
Answer/Response:
From the clinical chemistry lab for screening labs: Name, age, date
Samples collected during the study itself: Protocol #, Name, date

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

► **IF YES, list the information that will be deleted.**

EXAMPLE: name, medical record#. DO NOT STATE "ALL HIPAA IDENTIFIERS" SPECIFICALLY LIST WHICH ONES WILL BE DELETED.

Answer/Response:

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:

No - Not always, for example many of the insulin samples will be run in an assay together to eliminate possible variance between assays.

► **IF NO, where will the specimen be stored until analysis is done?**

INSTRUCTIONS: If at UVa will the specimen be stored in a refrigerator/freezer in a lab, a room-provide room number, or specific location).
To protect confidentiality, whenever possible, you should consider using a central facility/repository such as the UVa Biorepository and Tissue Research Facility.

Answer/Response:

UVA in freezer in core lab of CRU or our lab located in Fontaine Research Park 450 Ray C Hunt Drive, Room 1280 (IBC numbers 132-02 and 705-09 respectively).

Specimen Shipping

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

Answer/Response: No

Specimen Security

The following security precautions will be implemented:

- Specimens will be kept in a locked freezer/ or locked room

__X__ Specimens will be stored with HIPAA identifiers. Access to the freezer/room will be limited to authorized personnel. Specimens with HIPAA identifiers will never be shared outside of UVa without the written permission of the subject.

_____ Specimens will be stored with a code and no HIPAA identifiers. The key to the code will be kept in a different location than the specimens.

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

Compensation in Case of Injury

If a subject requests compensation for an injury, the study team should notify the IRB-HSR (924-9634/2439847) the UVa Health System Patient Relations Department (924-8315). As a proactive courtesy, the study team may also notify UVa Health System Patient Safety and Risk Management (924-5595).

On request, the study team should provide the Risk Management Office with the following information/documents:

- Subject Name and Medical Record Number
- Research medical records
- Research consent form
- Adverse event report to IRB
- Any letter from IRB to OHRP

Subject Complaints

During a research study, the study team may receive complaints from a subject. If the study team is uncertain how to respond to a complaint, or is unable to resolve it with the subject, the study team may contact the IRB-HSR (924-9634/243-9847), the UVa Health System Patient Relations Department (924-8315).

Request for Research Records from Search Warrant or Subpoena

If the study team receives a request for research records from a search warrant or subpoena, they should notify UVa Health Information Services at 924-5136. It is important to notify them if information from the study is protected by a Certificate of Confidentiality.

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