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Rationale and Trial Design of MesEnchymal Stem Cell Trial in Preventing Venous Stenosis of Hemodialysis Vascular Access Arteriovenous Fistula (MEST AVF Trial)

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Key Points:
*At one year after placement, 60% of hemodialysis VAF will develop venous neointimal hyperplasia (VNH) and subsequent venous stenosis (VS).

*Autologous adipose derived mesenchymal stem cells may help reduce venous stenosis formation associated with hemodialysis AVF.

*There are no therapies available to prevent venous stenosis formation associated with hemodialysis AVF.

Abstract:
Background: Hemodialysis arteriovenous fistulas (AVFs) are the preferred vascular access for patients on hemodialysis. In the Hemodialysis Fistula Maturation Study, 43.7% of the patients achieved unassisted maturation of their fistula without needing an intervention. Venous neointimal hyperplasia (VNH) and subsequent venous stenosis (VS) is responsible for lack of maturation. There are no therapies that can prevent VNH/VS formation. The goal of this paper is to present the background, rationale, and trial design of an innovative phase 1/2 clinical study that is investigating the safety of autologous adipose derived mesenchymal stem cells (AMSCs) delivered locally to the adventitia of newly created upper extremity radiocephalic (RCF) or brachiocephalic fistula (BCF). Methods: The rationale and pre-clinical studies used to obtain a physician sponsored investigational new drug trial (IND) are discussed. The trial design and endpoints are discussed. Results: This is ongoing trial which will complete this year. Conclusion: This is a phase 1/2 single center, randomized trial which will investigate safety and efficacy of autologous AMSCs in promoting maturation in new upper extremity AVFs.

Disclosures: A. Piryani reports the following: Other Interests/Relationships: American College of Physicians. A. Dietz reports the following: Ownership Interest: Mill Creek Life Science; Patents and Inventions: Mill Creek Life Science/Avobis; Scientific Advisor or Membership: Mill Creek Life Science/Avobis. All remaining authors have nothing to disclose.

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Key Points:

- At one year after placement, 60% of hemodialysis VAF will develop venous neointimal hyperplasia (VNH) and subsequent venous stenosis
- (VS).
- Autologous adipose derived mesenchymal stem cells may help reduce venous stenosis formation associated with hemodialysis AVF.
- There are no therapies available to prevent venous stenosis formation associated with hemodialysis AVF

Abstract:

Background: Hemodialysis arteriovenous fistulas (AVFs) are the preferred vascular access for patients on hemodialysis. In the Hemodialysis Fistula Maturation Study, 43.7% of the patients achieved unassisted maturation of their fistula without needing an intervention. Venous neointimal hyperplasia (VNH) and subsequent venous stenosis (VS) is responsible for lack of maturation. There are no therapies that can prevent VNH/VS formation. The goal of this paper is to present the background, rationale, and trial design of an innovative phase 1/2 clinical study that is investigating the safety of autologous adipose derived mesenchymal stem cells (AMSCs) delivered locally to the adventitia of newly created upper extremity radiocephalic (RCF) or brachiocephalic fistula (BCF).

Methods: The rationale and pre-clinical studies used to obtain a physician sponsored investigational new drug trial (IND) are discussed. The trial design and endpoints are discussed.

Results: This is ongoing trial which will complete this year.

Conclusion: This is a phase 1/2 single center, randomized trial which will investigate safety and efficacy of autologous AMSCs in promoting maturation in new upper extremity AVFs.

Introduction:

There are more than four million patients world-wide who have end stage kidney disease (ESKD) and the majority require hemodialysis for renal replacement therapy [1]. The National Kidney Foundation Kidney Dialysis Outcomes Dialysis Initiative (KDOQI) guidelines recommend that an autogenous arteriovenous fistula (AVF) be placed in patients as the preferred vascular access [2]. Despite the better patency of AVF when compared to polytetrafluorethylene grafts, approximately 60% of AVFs fail to mature due to development of a venous stenosis (VS) because of neointimal hyperplasia (VNH) of the outflow vein [3]. It is postulated that abnormal shear stress, hypoxic injury, inflammatory cytokines, matrix deposition and other factors cause a cascade of events that result in VNH/VS formation [3]. Multiple studies have focused on developing local therapies such as gene therapies, recombinant elastase (PRT-201), biological small molecule inhibitors and stem cells to prevent VNH/VS formation [4-12]. However, currently there are no therapies that can prevent AVF stenosis and reduce the need for costly invasive procedures such as angioplasty, stent, and other therapies.

Previous work from our laboratory and others utilizing experimental animal models of pigs, rats and mice has demonstrated a significant increase in the expression of pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1), CX3CR1 (C-X3-C Motif Chemokine Receptor 1), tissue necrosis factor-α (TNF-α), and others in the outflow veins of AVFs resulting in

VNH/VS formation [13-19]. The inflammatory process is thought to be one of the principle causes of VNH formation leading to access failure. However, biologic therapies such as adipose derived mesenchymal stem cells (MSCs) have not been tested clinically. Mesenchymal stem cells have generated interest for their potential application of treating vascular injury [10, 12]. Our lab has shown in preclinical study using immunodeficient mice that topical administration of human adipose derived MSCs to the adventitial surface of the outflow vein at the time of AVF creation attenuates the formation of VNH/VS, thereby improving AVF patency [12]. We used this preclinical data to obtain approval from the FDA and Mayo Clinic Institutional Review Board to perform a phase 1 randomized clinical trial in ESKD patients undergoing the placement a newly created upper extremity radiocephalic (RCF) or brachiocephalic fistula (BCF). The trial was registered on www.clinicaltrials.gov (NCT02808208).

The goal of this paper is to describe the trial design and discus the rationale for the clinical trial. The primary objective of this phase 1/2 clinical trial was to assess the safety of autologous adipose derived MSCs for use in ESKD patients undergoing the creation of a new upper extremity hemodialysis arteriovenous fistula. The secondary objectives were to assess the treatment effect of adipose derived MSCs on outflow vein remodeling, maturation, blood flow as assessed using serial ultrasound evaluation, patency, and reduction in the number of procedures needed to maintain vascular access patency.

Methods:

We obtained funding from the Mayo Clinic Center for Regenerative Medicine, NIH HL098967, and DK107870 to support the research and creation of this paper. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Institutional Review Board (IRB) and Investigational new drug (IND) approval with clinicaltrials.gov registration:

We obtained approval to perform a phase 1/2 randomized clinical trial from the FDA in the form of an Investigational Drug Approval (IND16884) and Mayo Clinic IRB approval (15-009053) in ESKD patients undergoing the placement of a new upper extremity RCF or BCF. The trial was registered on www.clinicaltrials.gov (NCT02808208) prior to beginning the clinical trial.

Trial overview and aim:

This was a randomized phase 1/2 clinical trial in which patients were randomized to either autologous adipose derived MSC treatment or no treatment at the time of surgical assessment for placement of an AVF. **Figure 1** shows the overall study design.

Preoperative vein mapping:

All patients underwent preoperative vein mapping prior to evaluation for surgical placement of hemodialysis AVF. The ultrasound (US) was performed using a Sequoia US in the outpatient center in the Gonda building. The US department has been certified by the Intersocietal
Commission for the Accreditation of Vascular Laboratories (ICAVL). Ultrasound of the upper extremity was performed to assess for suitability of veins (cephalic and basilic) and arteries (radial and brachial) for surgical creation of an upper extremity radiocephalic (RCF) or brachiocephalic fistula (BCF) [20]. In general, by US vein mapping for the placement of an RCF, a diameter of the radial artery greater than 2.5-mm or larger and a cephalic vein diameter of 2.0-mm or larger was required. For BCF placement, a brachial artery diameter of 3.0-mm or larger was required with a cephalic vein diameter of 3.0 mm or greater. After vein mapping, patients underwent assessment by a vascular or transplant surgeon for suitability of creation of an upper extremity surgical fistula. We had 8 different transplant and vascular surgeons who place RCF or BCF participate in the trial.

Outcome analysis:

Patients returned for follow up US after AVF creation at 1, 2, 3, 6 and 12 months later. We assessed for the development of stenosis at the anastomosis where

cells were delivered compared to controls including outflow vein remodeling and blood flow. The primary and secondary endpoints of the trial are listed in **Table 1**.

Primary endpoint:

The primary endpoint was safety at 4-week follow up based on infection, thrombosis, and patency of the AVF. This was based by clinical exam, CMP test, and ultrasound evaluation.

Secondary endpoints:

The secondary endpoints for each group included assessment of primary and secondary patency of the AVF, number of interventions performed to maintain patency, time to maturation as assessed by US and US assessment of diameter of outflow vein with blood flow.

Enrollment of patients:

Inclusion Criteria:

The inclusion criteria for the study included patients, 18-85-year-old, who were pre-dialysis or dialysis dependent requiring placement of a new upper extremity

brachiocephalic or radiocephalic fistula. We did not enroll patients requiring a brachiobasilic fistula. Patients in other investigational trials were not included.

Exclusion criteria:

Patients were excluded if they had active infection or were being treated for cancer. In addition, we excluded patients who had central venous stenosis in the extremity where the access was being planned.

Informed consent:

Patients eligible for the study were asked to enroll. Informed written consent was received, and the risk and benefits of the trial were explained to them.

Randomization of patients:

Patients were randomized using block randomization with size of two to either autologous adipose derived MSC or placebo with anatomic location of AVF (RCF or BCF), age (below 65 years vs 65 years and older) and gender as stratification factors.

MSC isolation from fat:

Patients in the adipose derived MSC group underwent a subcutaneous procedure to obtain adipose tissue to isolate and culture MSC cells. The samples were taken from the right lower quadrant. Briefly, the procedure was performed sterilely, and the skin was anesthetized with 1% lidocaine, followed by a small incision (~1-2 inch) made to remove approximately 1-5 g of subcutaneous fat was removed. The fat was used to isolate the MSCs. The incision was sutured.

AMSC Isolation and Characterization:

The fat derived MSCs from patients were isolated and cultured by the Immune, Progenitor, and Cell Therapeutics Lab (IMPACT) Lab at the Mayo Clinic as described previously [21]. The MSCs are CD73 (+), CD90 (+), CD105 (+), CD44 (+), and HLA-ABC (+).

Surgical creation of RCR or BCF AVF:

The surgical fistula was created as described previously elsewhere [2].

Stem cell administration:

After creation of the fistula, the diameter of the outflow vein was measured (**Figure 2**). The dose of stem cells that was delivered was based on the surface

area of outflow vein using the formula: [(π)(diameter in cm)(5cm) x (500,000 cells per cm^2]. Stem cells in Lactated Ringer's solution were dripped onto the outside of the distal radial or brachial artery 1 cm proximal to the anastomosis and extended onto the first 4 cm of cephalic vein just distal to the anastomosis. **Table 3** shows the total amount of stem cells delivered based on the different diameters of the cephalic vein. This data will be entered into a redcap database.

Follow-up:

All patients will return for follow up after their surgery. The schedule of events with the different evaluations are described at 7, 28 days, with US and laboratory values with clinical examination at 1, 2, 3, 6, and 12-months (**Table 4**).

US assessment of AVF maturation:

For BCF, maturation was assessed by ultrasound (US) and defined as matured when the cephalic vein diameter ≥ 6-mm with the cephalic vein within 6-mm of the skin surface, and a blood flow ≥ 600 mL/min [2].

For RCFs, we defined matured by US of the cephalic vein diameter ≥ 4-mm of the cephalic vein within 4-mm of the skin surface, and a blood flow ≥ 500 mL/min [22].

Safety and Adverse Events:

Patients will be evaluated for adverse events for one year after enrollment. The descriptions and grading scales are found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and will be utilized for AE reporting. Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to severity for the purposes of regulatory reporting to NCI. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Statistical Analysis: Descriptive summaries will be reported as median (minimum, maximum). Comparisons between the groups (stem cell vs. placebo) will be performed using Wilcoxon rank sum tests for continuous variables and using Fisher's exact test for categorical variables. Non-parametric tests will be used due to smaller sample size and non-normally distributed data. No adjustment for multiple comparisons will be done. Patency and maturation as time to event endpoints will be analyzed using Kaplan Meier Survival Curve analysis approach and median time to event and interquartile range will be presented. All tests will be two sided and *p*-values less than 0.05 will be

considered statistically significant. Analysis will be performed using SAS software version 9.4 (SAS Inc, Cary, NC, USA).

Discussion:

In 2017, there were ~750,000 US patients with end-stage kidney disease (ESKD) who required chronic hemodialysis (HD) [23]. The ESKD population will double in the next decade due to the increase in obesity and diabetes [23]. Optimal HD and clearance of uremic toxins requires vascular access through an arteriovenous fistula (AVF). Approximately, 40,000 AVFs are placed for hemodialysis in the US annually [23]. ~60% of AVFs will fail due to VNH/VS. More than four billion dollars is spent annually to maintain the optimal function of AVFs [24]. Unfortunately, there are no therapies which can prevent stenosis formation in hemodialysis AVFs.

Several factors have been hypothesized to cause VNH including shear stress, inflammation, oxidative stress, hypoxic injury to the vessel wall, and mechanical injury post AVF placement [3, 13, 15, 17, 25-35]. An ideal cellular therapy will be one that can be obtained in large numbers with anti-inflammatory and antiproliferative properties that can be with manufactured with good manufacturing process for use in clinical trials. Mesenchymal stem cells (MSCs) have been used to abrogate vascular injury. They have been isolated and expanded from several different sources, including bone marrow, adipose tissue (AMSC), and cord blood [36]. These cells have anti-inflammatory properties that can result in homeostasis, repair, and aid in regeneration in pathologic responses caused by vascular injury [37]. In other studies, investigators have demonstrated that MSC transplantation can reduce fibrosis in the heart, lung, liver, and kidney in experimental animal

models [38-43]. Along with having anti-inflammatory properties, MSCs can inhibit the proliferative effects of monocytes, tumor cells, and cardiac fibroblasts [44-47]. Finally, MSCs have been shown to reduce hypoxic injury after myocardial infarction because they home to regions of hypoxia [48, 49].

Previous studies have shown stem cells and progenitor cells can have beneficial effects on blood vessel remodeling and endothelial regeneration [50-52]. Our lab reported that autologous late outgrowth endothelial cells delivered to the anastomosis after placement of a hemodialysis polytetrafluoroethylene grafts could reduce venous stenosis in a porcine model [9] . We showed in cell culture that EPCs co-cultured with fibroblasts reduced phenotypic conversion of fibroblasts to myofibroblasts under hypoxic injury [53]. In a rat model, MSCs were shown to reduce carotid artery stenosis following arteriotomy [54]. Furthermore, the luminal area in MSC-treated carotid arteries was 36% greater than in control arteries. Optimizing vascular healing and remodeling around the arteriovenous anastomosis following AVF creation is crucial to minimize stenosis formation as justified by the fact that the juxta anastomotic is the most common location for AVF stenosis to occur [55]. In addition, reduced late remodeling at the anastomosis due to changes in vessel wall shear stress may be influenced by MSCs [56, 57].

Our laboratory has investigated the role of periadventitial xenotransplantation of 250,000 human adipose tissue-derived MSCs in an immunodeficient male mouse with carotid artery to jugular vein AVF has been shown to reduce expression of

the *Mcp-1* gene. This gene is involved in monocyte migration as well as lowering infiltration of CD68 (+) cells in the vessel wall [12]. In addition, the mean lumen vessel area increased by 176% at day 7 and 415% by day 21 with a reduction in proliferation and smooth muscle cells. Moreover, ^{89}Zr labeled MSCs were tracked using PET imaging and we observed that there was ^{89}Zr activity for up to 3-weeks after delivery.

There is limited available data regarding the cell transplant in human AVFs. However, a prior study by Conte et al investigated the use of allogeneic (human) endothelial cell implantation after dialysis access creation. V-HEALTH was a multicenter phase 1/2 trial assessing the safety of allogeneic endothelial cell implants (Vascugel) after the creation of arteriovenous access for hemodialysis use [58]. In phase 2, 57 patients (30 AVG and 27 AVF) were enrolled and randomized in a 2:1 fashion to receive either Vascugel or control matrices (placebo) at surgery. The study met its primary endpoint of safety as there was no difference in early complication rates between the Vascugel and placebo groups at 4 weeks (10.9% vs. 21.1% respectively). The adverse events observed were typical vascular access related complications or comorbidities associated with the ESRD population. The secondary endpoint was efficacy and there were no statistically significant differences in patency between the intent to treat groups at 24 weeks; however, the trial may not have been adequately powered to demonstrate a statistical difference. The authors found no significant difference in unassisted or assisted primary patency among AVFs or

arteriovenous grafts when compared to a placebo cohort. This indicates that MSCs may have a more robust role in prolonging dialysis AVF durability compared to other cell therapies. The present study will investigate the role of autologous adipose derived MSCs in preventing arteriovenous fistula failure by reducing VNH/VS formation.

Disclosures: A. Piryani reports the following: Other Interests/Relationships: American College of Physicians. A. Dietz reports the following: Ownership Interest: Mill Creek Life Science; Patents and Inventions: Mill Creek Life Science/Avobis; Scientific Advisor or Membership: Mill Creek Life Science/Avobis. All remaining authors have nothing to disclose.

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Author Contributions: Ameet Piryani: Writing - original draft. Sreenivasulu Kilari: Conceptualization; Data curation. Edwin Takahashi: Conceptualization; Formal analysis; Writing - original draft; Writing - review and editing. Randall DeMartino: Writing - original draft. Jay Mandrekar: Methodology. Allan Dietz: Writing - original draft. Sanjay Misra: Writing - original draft; Writing - review and editing.

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Figure and Table Legends:

Table 1: Inclusion and Exclusion Criteria

Table 2: Primary and secondary endpoints

Table 3: Total number of AMSCs delivered

Table 4: Schedule of events

Figure 1: Trial design

Figure 2: Intraoperative AMSC delivery. **A and B** show the extremity where the BCF will be placed. **C** is intraoperative delivery of AMCS after AVF creation.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria:

- Pre-dialysis or dialysis patients
- Age 18-85 years old
- New planned BCF or RCF
- Two stage fistulas not allowed
- Life expectancy of at least 2 years

Exclusion criteria:

- Active infection
- Central venous stenosis in the arm where the access is being planned
- History of cancer with ongoing treatment
- Participation in another study

Table 2: Primary and secondary endpoints

Primary endpoint:

Safety: Assessed based on infection, thrombosis, patency at 30-days

Secondary endpoints:

Kaplan Meier estimate of Primary patency, Secondary patency

Number of interventions performed per group

Time to maturation as assessed by US

US assessment of diameter of outflow vein and blood flow

Table 3: Number of adipose derived MSCs to be delivered at the AVF

Diameter of cephalic vein (cm)	Total number of AMSC delivered
0.3	2355000
0.4	3140000
0.5	3925000
0.6	4710000
0.7	5495000
0.8	6280000
0.9	7065000
1	7850000

Table 4: Schedule of events

Schedule of Events									
Study Activity	Screening (Visit 1)	Surgery (Visit 2)	7 Day (± 2 Days) (Visit 3)	4 week (± 5 days) (Visit 4)	8 week (± 7 days) (Visit 5)	3 month (± 14 days) (Visit 6)	6 month (± 14 days) (Visit 7)	12 month (± 14 days) (Visit 8)	Off Study [3]
Written informed consent	X								
History: Detailed or Brief	X		x	x	x	x	X	x	
Physical exam (Ht, Wt, BSA, VS)[1]	X							x	
Blood collection for CBC/ CMP	X			x					
Blood collection for Inflammatory Cytokines	X		x	x					
Ultrasound - Vessel Measurements and flow	X	x		x	x	x	X	x	
Outflow vein samples		x							
Brief Exam, Vitals and Adverse event evaluation		x							

1: CBC: Complete Blood Count; CMP: Complete Metabolic Panel
2: Inflammatory Cytokines: Pro: (TNF-α, MCP-1, IL-1β): Anti: (IL-10)
3: Off-study evaluation/ Every dialysis visit.

Description of Treatment Schedule:

Visit 1 (Day -42, Week -6, Screening and Baseline Evaluation)

Patients will be evaluated for eligibility and the study coordinator or team member in the Departments of Radiology, Nephrology or Surgery will obtain written informed consent. Subjects will be identified and randomized to one of two treatment groups based on a unique sequential number assigned after signing the consent form. Patients will undergo a detailed history and physical exam along with vital sign check. A CBC and CMP will be performed by Mayo Clinic Laboratory services. Two 20-mL samples of blood will also be collected for baseline inflammatory cytokines, centrifuged, and stored at −70°C in the Vascular and Interventional Radiology Translational Lab until analysis.

Patients will be scheduled for a vascular mapping ultrasound, meet with a vascular or transplant surgeon for vascular access evaluation and planning. Patients in AMSC treatment group 1 will also be scheduled for an adipose tissue biopsy to harvest and culture cells.

The adipose tissue biopsy (approximately 5g) will be performed in an outpatient surgical suite under sterile conditions. The tissue will be transferred to the Human Cell Therapy Laboratory located in Hilton Building, Mayo Clinic Rochester. Cells will be expanded ex-vivo using approved protocols. The total amount of cells will be calculated based on the approximate surface area of the outflow vein segment: [(2π)(radius in cm)(5cm) x 500,000cells per cm^2] = *n* (total cells required). In the event there is no cell growth from the tissue obtained from the biopsy, the patient may elect to have a second biopsy.

6.2.1.b Visit 2 (Day 0, Surgery)

<u>Pre-operatively:</u>
Patients will be admitted to St. Mary's or Methodist Hospital, Mayo Clinic. Vital signs (blood pressure, temperature, and heart rate) will be obtained; risk and benefits will be re-explained verbally. A designated team member will deliver the treatment agent for application.

<u>Intra-operatively:</u>
Patients will undergo surgical creation of an upper-extremity arteriovenous fistula as planned with their vascular or transplant surgeon. Vessel measurements and flow data using a transonic probe will be obtained prior to and after access creation. In addition, an outflow vein specimen will be collected and transferred for storage to the Biospecimens Accessioning and Processing (BAP) Lab and the

Vascular and Interventional Radiology Translational Lab . In the treatment group (1) AMSCs in 5ml RL solution will be applied to the juxta-anastomotic adventitial surface of the outflow vein as a series of drops (via injection) over a 5-minute period. All surgical information will be retained in the patient and trial records.

Post-operatively:

The patient will be transferred to the recovery room for observation (as a normal part of care) and closely monitored for signs of a treatment related reaction or infection. Please refer to protocol section 6.4 for reaction management. In the case of an unanticipated surgical outcome (e.g., failed access creation, AV graft placement instead of AV fistula creation), a replacement patient will be recruited to meet inclusion criteria and target accrual. If consent is provided, the original patient will still be followed up to evaluate the primary objective of safety if in the treatment group (1).

Visit 3 (Day 7 ± 2 days Follow-up after AVF placement)

Patients will return for follow-up in the outpatient clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A brief medical history including adverse event development will also be taken. Two 20-mL samples of blood will also be collected (non-surgical arm) for inflammatory cytokines, centrifuged and stored at −70°C in the Vascular and Interventional Radiology Translational Lab until analysis.

Visit 4 (Week 4 ± 5 days Follow-up after AVF placement)

Patients will return for follow-up in the outpatient clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A brief medical history including adverse event development will also be taken.

A CBC and CMP will be performed by Mayo Clinic Laboratory services. Additionally, a 40-ml sample of blood will also be collected (non-surgical arm) for inflammatory cytokines, centrifuged and stored at −70°C in the Vascular and Interventional Radiology Translational Lab until analysis. They will undergo an ultrasound to evaluate for access maturity, patency, outflow vein diameter, and blood flow rate.

Visit 5 (Week 8 ± 7 days Follow-up after AVF placement)

Patients will return for follow-up in the outpatient clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A brief medical history

including adverse event development will also be taken. They will undergo an ultrasound to evaluate for access maturity, patency, outflow vein diameter, and blood flow rate.

Visit 6 (Week 12 ± 14 days Follow-up after AVF placement)

Patients will return for follow-up in the outpatient clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A brief medical history including adverse event development will also be taken. They will undergo an ultrasound to evaluate for access maturity, patency, outflow vein diameter, and blood flow rate.

Visit 7 (Week 24 ± 14 days Follow-up after AVF placement)

Patients will return for follow-up in the outpatient clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A brief medical history including adverse event development will also be taken. They will undergo an ultrasound to evaluate for access maturity, patency, outflow vein diameter, and blood flow rate.

Visit 8 (Week 52 ± 14 days Follow-up after AVF placement)

Patients will return to for a final visit at Mayo Clinic. A brief examination will be performed of the AVF with vital signs (non-AVF arm). A medical history including adverse event development will also be taken. In addition, they will undergo a final ultrasound to evaluate for access maturity, patency, lumen geometry and blood flow rate. Patients will be assessed for changes in local hemodynamic wall shear stress and neointimal growth through changes in AVF lumen cross-sectional area and venous wall thickness.

Figure 1:

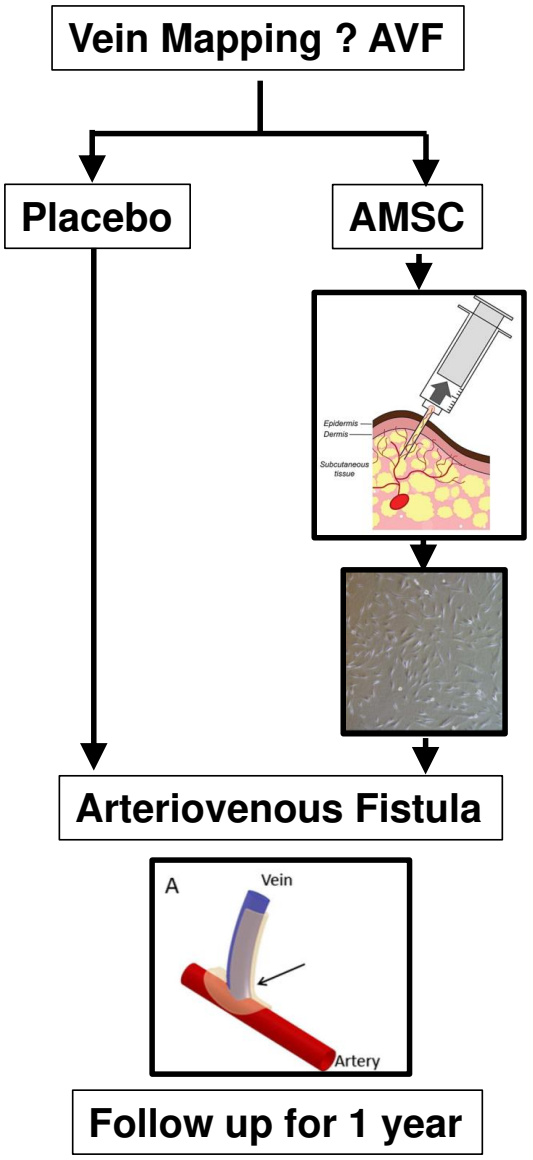
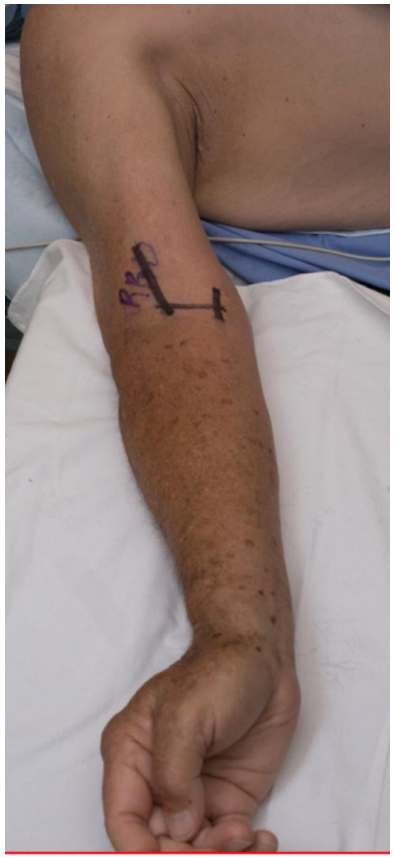
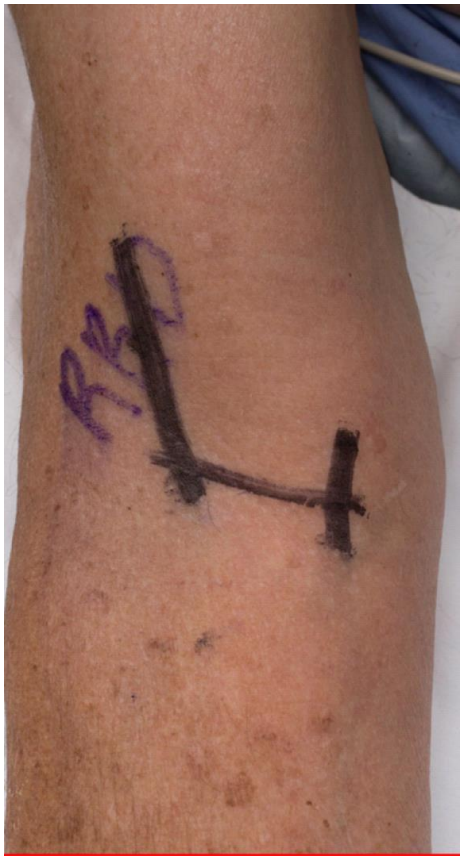

Vein Mapping ? AVF
Placebo
AMSC
Epidermis
Dermis
Subcutaneous tissue
Arteriovenous Fistula
A
Vein
Artery
Follow up for 1 year

Figure 2:

A.



B.



C.