Dialysis Access Consortium (DAC)

Manual of Operations

Graft Study

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Graft Study
(3/15/06)

1. RECRUITMENT

1.1 Purpose

To identify potential participants within the target population and educate them about the study in the hopes that they will be willing to enroll and participate.

1.2 Keys to recruitment

Keys to enhancing recruitment include: 1) early identification and contact of potential participants in the target population, 2) establishing rapport and 3) education about the vascular access and importance of the study. The following is an overview of the general procedures for patient recruitment into the study. These procedures will need to be adapted to fit the unique characteristics of each unit.

1.3 Target population

Any patient who gets a new arteriovenous shunt for hemodialysis is potentially eligible for this study. Thus the target population is patients already on dialysis (prevalent patients) or those who have chronic renal failure approaching the need for dialysis (incident patients).

1.4 Early notification

Recruitment will be enhanced by early and repetitive advertisement of the study to the target population and their providers. This can be accomplished in several ways:
Distribute short brochures describing the study to all current dialysis patients as well as patients in the clinic who have chronic renal failure and are likely to need dialysis within the next year.
Post signs in the dialysis units and clinics reminding patients and staff about the study.
Short “inservice” seminars, face-to face contact, letters or e-mails reminding nurses and physicians who work with dialysis patients and pre-dialysis patients about the study. Request their help in identifying and recruiting potential subjects.

1.5 Referral pattern leading to vascular access placement

Every study coordinator will need to familiarize themselves with the vascular access referral patterns at their own center. Typically, the nephrologist caring for the patient makes the referral for vascular access placement. In some settings, referrals may also originate from other health care providers (e.g. a physician-assistant or nurse in the clinic or dialysis unit or occasionally a non-nephrologist physician). Patients with chronic renal failure not on dialysis who are progressing to end-stage renal disease (incident patients) will typically be seen in the clinic or office. Referral for vascular access placement for these patients may occur at the time of a clinic appointment. However, referral may also be triggered between clinic appointments based on the results of new laboratory tests, patient symptoms or other patient-specific factors. Patients who are on dialysis (prevalent patients) may also be referred for placement of a new vascular access for a variety of reasons. The referral may occur because a prior vascular access is failing or has failed or because the patient needs to be converted from a central catheter to an arteriovenous shunt or because of conversion from peritoneal to hemodialysis. Understanding all the potential sources and sites of referral is critical to developing a plan to maximize early identification and recruitment of potential study participants.

For each nephrologist or nephrology group, practice patterns are generally established in which referral for access evaluation is made to a limited number of access surgeons. The patient will then see the vascular access surgeon who will make a recommendation on the type of access and probable location of the access. Scheduling the time for access surgery will depend on the surgeon's schedule, the availability of an operating room and the wishes of the patient. The time between the initial referral for vascular access placement and the ultimate surgical placement of a new access will be quite variable. In most cases it will take 1-4 weeks between the initial access referral and the access surgery. However, in some cases the time could be quite short, within 1-2 days. The study coordinator and principal investigator will need to track the number of these "fast-track" patients at each site, since special effort would be needed to identify and recruit these potential study participants.

1.6 Identification of potential study participants

Potential study participants could be identified and referred to the vascular access study coordinator at any step during the referral and evaluation process leading to vascular access placement. However, passive reliance on busy clinical staff who are not directly involved in the vascular access study to refer potential study participants is insufficient. Moreover, the multiple different sources of referral will make it difficult for the vascular access study coordinator to keep track of referrals from all these different sources in "real time." A better strategy to identify potential study participants is to develop a system where all referrals for vascular access evaluation come through a central source. The vascular access study coordinator can then refer to this source on a regular basis to identify potential subjects who need to be contacted about the study. The central source could be an access nurse coordinator who schedules patients for access evaluation, the receptionist who schedules appointments for the surgeon or surgical group or a computerized scheduling database. The availability of a computerized listing of all patients being referred for vascular access evaluation and the date of their appointment would greatly facilitate early identification and contact of potential participants.

1.7 Recruitment steps

Once a potential study participant has been identified then the study coordinator will need to contact the person to acquaint them with the study and determine whether they might be interested in participating. A key to recruitment is taking the time to establish rapport with the potential participant. Every effort should be made to contact the potential study participant as early as possible before they see the vascular access surgeon. This early contact will be very helpful for patients to give them more information about a vascular access and to give them time to think about their own participation in the study. If possible, the initial recruitment should involve a direct face-to-face contact between the study coordinator and the potential study participant. This contact could be either in the nephrology clinic or dialysis unit. However, this direct pre-enrollment contact will not always be possible. Alternative means for contacting potential participants before their scheduled surgery clinic appointment include a letter or a telephone call. Since it will not be known at this stage what type of access a patient might receive and we have a study for both types of access, then the same contact letter can be used for all potential study participants. An outline of what should be covered in this first meeting is shown below.

Items to be covered in the initial recruitment meeting.

1. Provide education about a vascular access and why it is needed for hemodialysis.
2. Discuss the two main types of vascular access (fistula and graft).

3. Inform the potential study participant about the problem of access clotting leading to loss of the access.
4. Inform the potential participant that we are conducting two research studies looking at study medications to determine whether a study medication might prevent clotting of their new access.
5. We will not know what study they would qualify for until they see the access surgeon.
6. Solicit and answer any questions.

Determine whether they might be interested in participating and whether we can contact them further about the study at the time of their appointment with the vascular access surgeon.
Provide contact information in case they have further questions.

If the potential study participant agrees to future contact then the vascular access study coordinator should contact them at the time of their evaluation by the vascular access surgeon. At this time, the type of vascular access that is planned should be known. If the potential study participant is to be scheduled for placement of a new arteriovenous graft, then they may be eligible to participate in the present Aggrenox Prevention of Access Stenosis Study. At this point the study coordinator should proceed with the enrollment phase of the study.

2. ENROLLMENT

2.1 Purpose

During the enrollment phase the potential participant is given more information about the study and then asked to sign a consent form if they understand and are willing to proceed. In addition, information is collected from the participant and their medical records to make sure that they meet qualification criteria to be in the study and to obtain baseline data that will be needed to interpret the results of the study.

2.2 Components

Enrollment consists of obtaining: 1) informed consent, 2) screening data, and 3) baseline data. To complete this phase and allow the participant to be randomized the following DAC forms must be completed.

Form 311 (screening form)
Form 312 (Baseline Dropout Form) if necessary
Form 322 (patient family, employment and income form)
Form 324 (baseline medication tracking form)
Form 331 (demographics, comorbidity and dialysis history form)
Form 333 (visit form)
Form 341 (quality of life form)
Form 351 (local biochemistry lab data form)

2.3 Who does the enrollment

The study coordinator or study investigator will do all phases of the enrollment. The study personnel who do the enrollment must have training in human subjects research. They must be listed as study participants on the local Institutional Review Board (IRB) application for this project as well as on the informed consent document. A trained data entry person, the study coordinator or study investigator may enter the enrollment data into the DAC database. Any person who does the data entry must have a password to the DAC database.

2.4 When and where will enrollment take place

This will depend on the recruitment plan at each site. The location for enrollment may be varied to meet the needs of the patient and study personnel. A good time for enrollment would be just after the potential participant sees the vascular access surgeon. At this time it will be known what type of access will be attempted and when the surgery will be scheduled.

2.5 When should enrollment be completed

Optimally, enrollment will be done the week prior to the access surgery and the patient should be randomized immediately after surgery. The time window for completing the enrollment data is up to 45 days before randomization. Enrollment must be completed no later than 2 calendar days after the access surgery in order for the participant to be randomized into the study. Baseline biochemical studies (hemoglobin, platelet count, serum albumin on DAC study form 351) must be done no more than 45 days before surgery. If more than 45 days elapses between completing the enrollment forms and surgery then a new set of DAC enrollment study forms must be completed with any updated information. In addition, if more than 90 days elapses between signing the consent form and surgery then the participant must be re-apprised about the study and a new consent form must be signed.

2.6 Required personnel training

All study personnel who are involved in carrying out the study plan must have received training and be certified in human subjects research as designated by their local Institutional Review Board (IRB). Personnel who perform enrollment must have read and be familiar with the Study protocol, DAC Study forms and this Manual of Procedures. In addition, all personnel who perform data entry must be familiar with how to enter data into the DAC database and have a valid password to enter the database.

2.7 Training and certification

Training and certification of training in human subject research will be done as specified by the local IRB overseeing research at each study site. Questions regarding human subject research should be referred to the Chairperson of the IRB at the study site. It is the responsibility of the Principal Investigator at each site to assure that study personnel at that site receive proper training in the study protocol and procedures and that the personnel are qualified to conduct human subjects research. Assistance with the protocol and forms can be obtained from the DCC or the Principal Investigator at each site. The DCC will provide assistance and training in the use of the DAC access database. Questions or problems with using the DAC database or obtaining a password should be referred to Barb Weiss or Jennifer Gassman at the DCC. Questions about medical care or medications should be directed to the Principal Investigator for the study site.

2.8 Detailed description of each of the three major components of the enrollment phase (informed consent, screening and baseline data).

2.8.1 Informed consent

2.8.1.1 Purpose

The informed consent provides documentation of the agreement to participate in a study, but it is only one part of the consent process. The entire informed consent process involves: 1) giving a subject adequate information concerning the study, 2) providing adequate opportunity for the subject to consider all options, 3) responding to the subject's questions, 4) ensuring that the subject has comprehended this information, 5) obtaining the subject's voluntary agreement to participate and, 6)

continuing to provide information as the subject or situation requires. To be effective, the process should provide ample opportunity for the investigator and the subject to exchange information and ask questions. (Paragraph modified from the FDA website).

2.8.1.2 Obtaining the consent

The consent should be obtained by a face-to-face meeting between the study coordinator or study investigator and the potential participant. Participation of other family members or trusted advisors for the potential participant in the consent process should be encouraged. The informed consent document approved by the local IRB must be available to the potential participant to look at and review while each item is being discussed. The potential participant must be given adequate time to review the document and ask questions before signing the consent. Consent can be done by telephone if the potential participant has an exact copy of the consent to review during the conversation. In this situation the potential participant can then return the signed and dated consent by either FAX or regular mail. However, the signed copy must be received before the enrollment process can be completed and the subject randomized into the study. There is no valid method for performing the consent by e-mail at this time. A witness must be present for the entire consenting process IF the consent is done orally using a short form. However, a witness to the signature is not mandatory if the full IRB-approved consent form written for this study is used and a copy is provided to the potential participant to review during the consent process. As soon as the clinical center has the signed consent, a copy of the signature page with the patient name "whited out", ID and namecode, and study name should be faxed to the DCC.

2.8.1.3 Details to be covered in obtaining the informed consent document

(Modified from the informed consent document).

Education about a vascular access graft – Describe a vascular access and why it is needed for hemodialysis.
Explain that a vascular access graft involves inserting a synthetic piece of tubing between an artery and vein to create an access for hemodialysis.
Inform the potential study participant about the problem of access clotting leading to loss of the access. This clotting is due to the build-up of tissue in the access typically at the connection between the arteriovenous graft and the vein. The build-up of tissue leads to slowing of the blood flow and this leads to clotting of the access. In this country, approximately half of the people who get a vascular access graft will have their first access failure within 1 year.

Purpose – The purpose of this study is to evaluate the use of the drug Aggrenox (a combination capsule of dipyridamole and aspirin) compared to a placebo (a capsule with an inactive substance) in subjects with newly created arteriovenous grafts to determine whether it improves long-term survival of the vascular access.

Discuss the study procedures. We expect a participant to be involved in the study for about 1 year but the involvement could be as long as 4 years. Participation in the study begins just after the creation of a new arteriovenous graft, and will continue until one month after the access fails or until the study ends. Participants who are scheduled to receive a new arteriovenous graft will be randomly selected (like drawing straws) to receive either Aggrenox or placebo (inactive substance). Participants in this study should not agree to participate in any other research trial while in this study. The study is divided into screening, randomization, treatment and follow-up phases. Discuss each of the phases.

Screening - Before entering the study, the participant will be asked questions about his/her medical history and undergo a physical examination to determine whether they are eligible to participate in the study. In addition, their medical records will be reviewed and laboratory tests checked to determine their eligibility.

Randomization - If the study team believes that the patient qualifies to participate in the study, then shortly after you confirm that the patient has a new arteriovenous graft placed he/she will be randomized to receive either the medication Aggrenox or a placebo (an inactive substance). Half of the participants will receive Aggrenox; the other half will receive the placebo. The assignment to medication or placebo is made in advance at the study's Data Coordinating Center at the Cleveland Clinic by a process similar to drawing straws. Neither the patient, nor the doctor, nor other research personnel will know whether the patient is taking medication or placebo. However, the medication assigned to the patient can be determined by the physician in case of a medical emergency by communicating with the study's Data Coordinating Center. This is an important option that is available in order to protect the patient's safety.

Treatment and follow-up - The participant will receive either Aggrenox or a matched placebo capsule twice a day by mouth starting as soon as possible after surgery and no later than 2 days after their surgery. The research team will follow them by the standard plan of care for patients with arteriovenous grafts. This follow-up will take place either in the dialysis unit or in the clinic. The capsule should be taken twice a day with water (at home). All unused drug and empty bottles must be returned to the research staff when a new supply of medication is provided or at the end of their participation in the study.

Typically after 3-6 weeks, their graft should be ready for use for hemodialysis (after swelling has decreased and the wound has healed). The decision to use their graft will be made by their dialysis physician and will not be influenced by their involvement in this study. During the entire study period, their physician and the research team using standard practices will monitor their graft on a regular basis. If there is evidence of the graft losing function, an angiogram will be done to look for narrowing in the graft that would lead to access failure. An angiogram is an x-ray study that involves injecting dye into the graft to determine if there is narrowing. If a significant narrowing is found then angioplasty will be recommended to dilate the narrowing. Angioplasty involves placing a balloon catheter into the lumen of the graft and inflating the balloon to dilate the narrow region. If their graft should clot, various procedures such as thrombolysis, thrombectomy or surgical repair of the graft can be done at the discretion of their treating physicians to attempt to save the graft. Thrombolysis and thrombectomy are procedures in which a catheter is used to attempt to break down or extract the clot. If adequate flow in the access can be restored then the vascular access graft will continue to be used for dialysis. If not, then a new access will be surgically created or other options for providing care will be arranged by their regular dialysis physician. This is the standard of care.

The participant will have the blood flow in their vascular access graft measured at regular intervals during the study. A drop in access blood flow is a sensitive way to determine whether a significant narrowing is developing in the graft. This technique is a standard of care used in some hemodialysis units to monitor vascular access function for all their patients. This procedure takes about 15-20 minutes and is done during the time of one of the regularly scheduled dialysis sessions. To do the measurement, the flow of blood in the dialysis circuit is reversed and a small quantity (a few tablespoons) of sterile saline is injected into the dialysis tubing. Special sensors placed on the tubing are used to determine the dilution of the saline by blood in the access and thereby calculate the access blood flow. The procedure uses the needles already inserted into the vascular access for dialysis and no blood is removed from the subject for this measurement. The first measurement will be done within 2 weeks of starting hemodialysis and a second measurement will be obtained

approximately 2 weeks later. Thereafter, the access blood flow measurements will be done monthly until the end of their participation in the study. This information will be recorded as part of the study and also available to their physician and other dialysis providers. If the vascular access blood flow meets established criteria indicating a high risk of significant narrowing then they will be referred for an angiogram of the access to determine the severity of the narrowing and whether balloon angioplasty is indicated.

Once a month during the time they are in the study, a member of the research staff will interview and examine them to determine whether there have been any problems with their vascular access graft or the study medication. The research staff will record the medications and dosages that they are taking and will assess their compliance with taking the study medication. At this time the research staff will also review their medical records and routine lab results from their dialysis unit or renal clinic. Any hospitalization, access-related procedure, episode of bleeding or other significant medical event thought to be related to the study medication will be recorded. If at any time the study team feels that the drug therapy is causing a side effect, the medication may be stopped and the standard care for patients on hemodialysis with arteriovenous grafts will be offered. Each monthly study visit will take about 30 minutes and this generally will occur when they are on dialysis or come to clinic for their regular evaluations. However, if they have not started on dialysis within 1 month after having the new access placed, then special arrangements will need to be made with the research study coordinator for a monthly evaluation until they start on dialysis.

Every three months during the time they are on the study the study coordinator or study physician will conduct a Quality of Life Questionnaire. This will consist of 3 questions about how they have been feeling since their graft was created. They are free to skip any questions that they do not wish to answer.

Their participation in the study will end one month after the first failure of their new vascular access graft or when the study ends, whichever comes first. A vascular access failure means the access has clotted or a procedure such as angioplasty is performed to prevent graft failure. If their access fails, then procedures will be performed to restore its function as described above. Once their participation in the study ends they will continue to receive the standard of care for all patients on hemodialysis provided by their regular dialysis physician.

A panel of experts called the Data Safety and Monitoring Board will monitor the results of the study. If the Board determines that there have been too many complications in the study or that the results of the study are determined, they will recommend that the study be stopped. This Board offers important protection to the participant as they participate in this research.

Discuss the study medication, Aggrenox. Aggrenox is an FDA-approved medication for the prevention of stroke in patients who have had a prior stroke or near stroke. The components of Aggrenox, aspirin and dipyridamole have been used individually and in combination to prevent arterial clotting that leads to a heart attack or stroke. Even though both of these medicines have been used in many patients, the combination medication Aggrenox has not yet been approved for prevention of clotting in arteriovenous grafts.

Review the possible risks from participating in this study.
Medication side effects. Discuss that Aggrenox may help their medical problem but also can cause side effects. The two active medications in Aggrenox, dipyridamole and aspirin, are widely used and have well-characterized side effects and risks, including an increased risk of bleeding, gastrointestinal disturbances and headache. However, it is not possible to predict whether they will experience some or none of these side effects. Information about the possible side effects of treatment with Aggrenox

is based upon the experiences of the men and women who have taken this medication in the past. Side effects usually stop when treatment with Aggrenox stops. However, there is a possibility that some side effects may remain for a long time or develop after stopping treatment.

Risk of bleeding. Discuss the risk of bleeding with the combination of aspirin and dipyridamole in Aggrenox. Dipyridamole is a weak blood-thinning medicine, but several studies show that it does not significantly increase the risk of bleeding over aspirin alone. In one large study of more that 6,000 patients without kidney failure, bleeding occurred in 3.6% of patients on Aggrenox compared to 3.2% on aspirin alone, 1.5% on dipyridamole alone and 1.3% on placebo. The overall risk of bleeding may be higher in patients with kidney failure. One study reported that bleeding occurred in 5% of dialysis patients on placebo and 8.4% of dialysis patients on Aggrenox. No patients were reported to have died from bleeding and the overall survival rate for subjects on Aggrenox was better than for those on placebo. These studies suggest that Aggrenox is likely to be safe and reasonably well tolerated. We anticipate that the risk of bleeding with Aggrenox will be increased when it is used in combination with other blood thinning medications, such as coumadin or anti-inflammatory medicines, such as Motrin (ibuprofen). If the participant requires any of these types of medications during the course of the study, the research team will discontinue the study capsules. They may take aspirin if their physician has recommended this. Tylenol is also okay to take for headaches, fever and pain when they are on Aggrenox.

Avoiding allergies or adverse drug interactions. The participant should not take Aggrenox if they have an allergy to aspirin or to dipyridamole. A known hypersensitivity reaction (e.g., asthma, anaphylaxis or urticaria) to a non-steroidal anti-inflammatory medication (e.g., Motrin) may indicate a hypersensitivity to aspirin and this person should be excluded unless it is known that they can tolerate aspirin. Aspirin allergy is sometimes seen in people with combination of asthma, sinus congestion and nasal polyps. If they have this combination of symptoms they should not participate in the study.

Peptic ulcer disease and other GI effects. Aggrenox can exacerbate peptide ulcer disease. If they have active peptic ulcer disease they may not participate in this study. Other side effects of Aggrenox that can occur include abdominal discomfort, heartburn, nausea or vomiting.

Other side effects. Aggrenox may cause other side effects, including headache, dizziness or angina.

Risk to embryo, fetus or infant that is breast-feeding. Discuss that it is not known whether Aggrenox may harm an embryo or fetus or an infant who is breast-feeding. It is not known whether treatment with Aggrenox may lead to birth defects.

Exclusion of women who are pregnant or breast-feeding. Discuss that a woman who is pregnant or is breast-feeding an infant may not participate in this research. A pregnancy test will be performed for any woman who has neither been amenorrheic for the previous 12 months nor surgically sterilized and who is sexually active and not using an acceptable means of birth control and wishes to participate in this study. A pregnancy test may be repeated later during the study for safety. If the subject is a woman who can bear children and suspects pregnancy during the time they receive treatment in this study, they must notify the study staff immediately. Their participation in this research will stop and a new plan of treatment arranged.

Avoiding pregnancy. Discuss that pregnancy should be avoided while they receive medications in this study. The study team will discuss appropriate ways to avoid pregnancy. If their method of avoiding pregnancy changes while they receive treatment in this study, it is their responsibility to inform the study team as soon as possible. Their participation in this research may stop, and the study team will help arrange a new plan of care.

Possibility of receiving placebo. Discuss that the participant may get a placebo. If they receive a placebo, they will not receive active medication for their condition. If their condition becomes

worse, their participation in the study may stop. If this happens, their doctor can discuss alternative care with them.

Risk of blood tests. Discuss that blood tests will be done on occasion. They may experience discomfort, bleeding, and/or bruising. They may feel dizzy or faint. On a rare occasion, an infection may develop at the site where the blood was collected.

Unforeseen risks. Discuss that there can be unforeseen risks and a previously unknown side effect may occur. A side effect may occur because of an interaction of Aggrenox with other medications they take (prescribed or over-the-counter) or may result from their participation in the study. It is not possible to estimate the chances of such occurrences or their severity.

Ways to reduce risks. Discuss ways they can reduce some of the risks. Ask questions about anything they do not understand. Keep appointments. Follow the doctor's recommendations. Tell the doctor about all prescriptions, non-prescription and herbal medications they are taking. Keep us informed if their telephone number changes. Stores pills in a safe place away from anyone who is unable to read and understand labels, especially children. Tell their study doctor before taking any new prescription, non-prescription or herbal medication even if another doctor for a different medical problem prescribes the medication. Tell their regular doctor that they are participating in this study.

If problems arise. Discuss what they should do if they have problems. If they experience unusual symptoms or pain at any time during their participation in the study, the study staff can recommend treatment. Ask them to report the problem to the study staff promptly. Point out the contact information on the consent and let them know you will provide a card with contact information on it for them to keep.

Benefits of study participation. Discuss that there may be no personal benefit for participating in this study. In the future, other people on hemodialysis may benefit from the results of this research. New information derived from this study may lead to improved medical care.

Alternatives to the study. Discuss the alternatives to participation in the study. Rather than participating in this study, the alternative is to have the usual care given to patients that get a vascular access graft for hemodialysis. While Aggrenox is available by prescription to patients who do not participate in the study, it is not currently FDA approved for this indication. The usual care does not currently involve giving Aggrenox or any other similar medication after surgery. At this time, the usual care for a clotted or failing graft is to modify the existing graft if possible, or perform a new surgery to place either a new access or a catheter for dialysis. If the person decides to participate in this research, but later changes their mind, they may receive the alternative care.

Conditions under which a participant may be withdrawn from the study without their consent. Their participation may be ended if their doctor believes that their participation in this study is not safe or if they are placed on a blood thinning medication such as coumadin, or an anti-inflammatory medication such as Motrin. Their participation may also be stopped if the sponsor or the Food and Drug Administration stops the study for safety or the sponsor cancels the study. Finally, their participation may be stopped if they fail to keep appointments or fail to follow the study procedures recommended by the study doctor.

If their participation in this research is stopped for any reason, it is their responsibility to come to the clinic for evaluations and discussion about future treatment. At that time, they need to return any unused study medication, including empty containers.

Costs for participating. Discuss costs for participating in this study. They will not be charged for study medication, study-related blood work, or study visits. Expenses related to angiograms, angioplasty, and procedures to open a clotted graft are their responsibility or the responsibility of their insurance provider. Because these procedures are standard practice in the medical community insurance providers typically cover them. Discuss if your center will cover parking fees. There are no study funds available to pay for transportation to and from the clinic, lost time away from work and other activities, lost wages, or child care expense.
Payment for participation. Discuss that there is no payment for participating in the study.

Participation is voluntary. They have the right to agree or refuse to participate in this research. If they decide to participate and later change their mind, they are free to discontinue participation in the research at any time. Refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled. Refusal to participate will not affect their legal rights or the quality of health care that they will receive at this center. Any significant new information that becomes available during their participation in the research and may affect their health, safety, or willingness to continue in the study will be given to them.

The right to confidentiality and privacy and how that will be protected. All information obtained from this research that can be identified with them will remain confidential within the limits of the law. The investigators will release such private information only to the sponsor. Representatives of the FDA, other U.S. and foreign government agencies and the sponsor may review and photocopy their medical and research records to assure the quality of the information used in the research. The results of this research may appear in scientific publications without identifying them by name.

We need to record all of their hospitalizations and other important medical events that take place while they are in the study and for five years after the end of the study. For this reason we will ask to record their Social Security number. Their Social Security number will be kept secure. They may refuse to give their Social Security number and still participate in the study.

An Institutional Review Board (IRB) is a group of people who are responsible for assuring the community that the rights of participants in research are respected. Members and staff of the IRB at this medical center may review the records of their participation in this research. A representative of the Board may contact them for information about their experience with this research. If they wish, they may refuse to answer any questions the representative of the Board may ask.

Compensation for injury. Discuss the issue of compensation for any injury that might be sustained while participating in this study. In the event of injury, medical treatment is available at the your institution. There is no compensation for treatment of research-related injury available from your center unless the injury is proven to be the direct result of negligence by an employee of your center. Should a research-related injury occur, the participant and/or their medical or hospital insurance carrier must pay for the cost of the treatment.

Encourage questions. Let them know that the study staff is available to answer their questions about this research. The Chairperson of the IRB is available to answer questions about their rights as a participant in research or to answer their questions about an injury or other complication resulting from their participation in this research. Provide them the telephone number where the Chairperson of the IRB can be contacted during regular office hours.

Sign the consent. Remind the participant that they can withdraw their consent to participate at any time. If they are willing to proceed with the study then have them sign and date the consent. Then the

person who obtained the consent should sign and date the consent on the appropriate lines below the participant's signature.

2.8.2 Screening data (DAC study form 311)

2.8.2.1 Purpose

Inclusion criteria focus the study on relevant subjects within the target population who are likely to benefit from use of the study medication. Exclusion criteria are established to exclude subjects who might be at excessive risk from participation, those who are unlikely to comply and unusual subjects who might introduce bias in the results if they were randomized unequally between study groups. During the screening process, data will be collected to determine whether a potential participant meets criteria for inclusion in the study and does not meet any of the criteria that would exclude them from participation in the study.

2.8.2.2 Inclusion criteria

Inclusion criteria are designed to focus the study on relevant subjects within the study population who are likely to benefit from use of the study medication. Enrollment for this study is open to both incident as well as prevalent adult hemodialysis patients who receive a new arteriovenous graft (either synthetic or biograft) and are able to give informed consent. The major goal of the study is to prevent the development of access stenosis. Limiting enrollment to subjects who receive a new arteriovenous graft (as opposed to including patients with prevalent grafts) maximizes the likelihood of preventing stenosis and is relevant to clinical practice. Starting Aggrenox when a new access is created mimics the protocol that worked in a previous pilot study by Sreedhara et al. More importantly, starting the study medication early maximizes the opportunity for Aggrenox to work by any of its proposed mechanisms of action, including inhibition of the smooth muscle proliferation that leads to the development of access stenosis or by decreasing platelet aggregation and thrombosis.

The inclusion criteria are as follows.

Age equal or greater than that at which consent can be obtained without parental involvement.
Rationale – Most people on dialysis are over the age of 18. Subjects under the age of 18 are a potentially vulnerable population who are less likely to get an arteriovenous graft and less likely to benefit from inclusion into this study.
Age of Majority - State law applicable at the study site defines the Age of Majority in which a person can legally consent without parental involvement. Depending on the State, the Age of Majority will be between 18-21 years of age.
DAC study requirement - The potential participant must be of the Age of Majority on or before the date the informed consent is signed.
Documentation of age in the DAC study – DAC study form 311 will determine whether a potential subject is at least 18 years of age, which is the current Age of Majority in most states. It is the responsibility of the study personnel at a participating site to know the Age of Majority in their state and to not enroll subjects who are under age.

Life expectancy of at least six months.

a. Rationale - Enrolling subjects who die rapidly would limit the ability to see an effect of the study medication and may bias the study results.
b. How to determine life expectancy - This is a judgement made by the study personnel based on a global assessment of the potential participant. It can best be determined by talking with the

potential subject and their family about the person's current functional status and observing them in clinic. Do not base this decision simply on the list of patient diagnoses. If a person is living independently and able to care for themselves they have an excellent chance of living more than 6 months. If they require help with minimal activities of daily living such as eating, going to the bathroom and bathing, then questions should be raised about the person's ability to survive and participate in the study. Generally, persons who are in a hospice for terminal cancer or who have such severe heart failure that they can not get out of a chair or bed by themselves, would not be candidates to enroll into the study. If there are questions, then consult the potential subject's primary care provider or the Principal Investigator at the study site. If a potential subject's life expectancy is uncertain the study personnel should err on the side of enrolling them into the study.

Chronic renal failure with anticipated start of hemodialysis within six months of enrollment or current dialysis-dependence.

a. Rationale – The study is designed to examine the effect of Aggrenox on access failure in subjects who are undergoing regular hemodialysis. Subjects who do not have their access cannulated on a regular basis may have a different rate of access failure. Moreover, the study protocol calls for routine monthly monitoring of access blood flow and visits with the study coordinator. If a subject is not on dialysis then it will not be feasible to monitor their access flow and much harder to accurately determine the exact time of any access failure, which is the primary outcome of the study.
b. How to determine anticipated start time for dialysis – Most persons who are not on dialysis and receive an arteriovenous graft would be expected to start on dialysis within a few weeks of the time they get the graft. The presence of uremic symptoms (e.g. poor appetite, nausea, vomiting, pruritis or severe volume overload), hyperkalemia, or a calculated creatinine clearance less than 15 ml/min are good indicators that dialysis will be started soon. If the study coordinator has a question about whether a potential participant is likely to start dialysis within 6 months then they should contact the patient's primary nephrologist or the Principal Investigator at the study site.

A new or planned AV graft placed in any location for the purpose of hemodialysis.
Rationale – While upper arm straight grafts tend to have a better survival than forearm grafts (of any configuration), grafts placed at other sites such as the leg appear to have a survival similar to upper arm grafts.
Type of access material - Any type of graft material and any configuration of the access is acceptable. Even though most arteriovenous grafts are created using synthetic material (e.g. Gore-tex, Impra), there is currently no evidence that the biology of access failure is any different in arteriovenous grafts composed of any other material (e.g., biografts).
Source of information – Contact the surgeon who placed the graft if there is a question on the type of material used or the location of the graft.

The patient is expected to stay at a participating dialysis facility for at least 6 months.
Rationale – Excessive patient drop-out rate can affect the power of the study to detect a significant effect of the study medication.
Method of assessment – Query the potential subject on whether they expect to stay at the participating dialysis unit for at least 6 months. If there is a chance of the participant getting a renal transplant then inquiry as to the subject's current transplant status and where they are on the transplant waiting list.

The patient's physician(s) will allow the patient to participate.

a. Rationale – Obtaining the consent of the person's personal physician is important because: 1) the physician may have information about the potential subject's medical condition that would prevent them from participating in the study, 2) the physician needs to know that their patient will be on a study medication to monitor for adverse events and avoid potential adverse drug interactions and 3) the personal physician can be an ally in encouraging compliance of the subject with the study medication,

b. Method of assessment – The study coordinator or study investigator should contact the potential participant's primary physician directly to obtain their assent to enroll their patient in the study. In most cases, the primary physician will be the nephrologist who referred the patient for the access placement or who follows the subject in the dialysis unit.

Ability to give informed consent. See section on informed consent in section 2.8.1, above.

Graft Template Consent

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	**Aggrenox Prevention of Access Stenosis**	
Sponsor:	National Institutes of Health/NIDDK	
Investigators:	Telephone No. (regular office hours)	Telephone No. (other times)
[Names here]		

INVITATION: Because you will soon have an arteriovenous graft placed as a vascular access for hemodialysis, you may be eligible to participate in this research study. Medical research involves offering a plan of care to a group of patients, collecting and studying information about each patient's experience, and using that information to develop the best possible care for future patients. The sponsor plans to include in this study more than 1,200 patients in the United States who get a new vascular access graft for hemodialysis.

PURPOSE: A common procedure that patients require for hemodialysis is placement of an arteriovenous graft in your arm to provide simple access to your bloodstream. This is called a vascular access graft. Unfortunately, nearly all hemodialysis patients who have arteriovenous access grafts experience problems with graft failure due to clotting. The purpose of this study is to evaluate the use of the drug Aggrenox (a combination capsule of dipyridamole and aspirin) compared to a placebo (a capsule with an inactive substance) in subjects with newly created synthetic grafts to determine whether it improves long-term survival of the vascular access.

PROCEDURES: If you agree to participate, your involvement in the study will likely last 1 year but could be as long as 4 years. Your participation in this study will begin around the time of surgery for placement of your synthetic graft. You will remain in the study until one month after your new graft fails or the study ends. Subjects who are scheduled to receive a new synthetic graft will be randomly selected (like drawing straws) to receive either Aggrenox or placebo (inactive substance). You should not agree to participate in any other research trial while you are participating in this study. The study is divided into screening, randomization, treatment and follow-up phases.

Screening: Before you enter this study, you will be asked questions about your medical history and undergo a physical examination to determine whether you are eligible to participate in the study. In addition, your medical records will be reviewed and laboratory tests checked to determine your eligibility.

Randomization: If the study team believes that you qualify to participate in the study, then shortly after you have a new vascular access graft placed you will be randomized to receive either the medication Aggrenox or a placebo (an inactive substance). Half of the participants will receive Aggrenox; the other half will receive the placebo. The assignment to medication or placebo is made in advance at the study's Data Coordinating Center at the Cleveland Clinic by a process similar to drawing straws. Neither you, nor your doctor, nor other research personnel will know whether you are taking medication or placebo. However, you should know the medication assigned to you can be determined by your physician in case of a medical emergency by communicating with the study's Data Coordinating Center. This is an important option that is available in order to protect your safety.

Treatment and Follow-up: You will be given either Aggrenox or a matched placebo capsule twice a day by mouth starting as soon as possible but no later than 2 days after your surgery. Then the research team will continue to follow you by the standard plan of care for patients with arteriovenous grafts. This follow-up will take place either in the dialysis unit or in the clinic. The capsule should be taken twice a day with water (at home) after proper instruction from the study staff. All unused drug and empty bottles must be returned to the research staff when a new supply of medication is provided or at the end of your participation in the study.

Typically after 3-6 weeks, your graft should be ready for use for hemodialysis (after swelling has decreased and the wound has healed). The decision to use your graft will be made by your dialysis physician and will not be influenced by your involvement in this study. During the entire study period, your graft will be monitored on a regular basis by your physician and the research team using standard practices. If there is evidence of your graft losing function, an angiogram will be done to look for narrowing in the graft that would lead to access failure. An angiogram is an x-ray study that involves injecting dye into the graft to determine if there is narrowing. If a significant narrowing is found then angioplasty will be recommended to dilate the narrowing. Angioplasty involves placing a balloon catheter into the lumen of the graft and inflating the balloon to dilate the narrow region. If your graft should clot, various procedures such as thrombolysis, thrombectomy or surgical repair of the graft can be done at the discretion of your treating physicians to attempt to save the graft. Thrombolysis and thrombectomy are procedures in which a catheter is used to attempt to break down or extract the clot. If adequate flow in the access can be restored then the vascular access graft will continue to be used for dialysis. If not, then a new access will be surgically created or other options for providing care will be arranged by your regular dialysis physician. This is our standard of care.

All subjects in the study will have the blood flow in their vascular access graft measured at regular intervals during the study. A drop in access blood flow is a sensitive way to determine whether a significant narrowing is developing in the graft. This technique is a standard of care used in some hemodialysis units to monitor vascular access function for all their patients. This procedure takes about 15-20 minutes and is done during the time of one of the regularly scheduled dialysis sessions. To do the measurement, the flow of blood in the dialysis circuit is reversed and a small quantity (a few tablespoons) of sterile saline is injected into the dialysis tubing. Special sensors placed on the tubing are used to determine the dilution of the saline by blood in the access and thereby calculate the access blood flow. The procedure uses the needles already inserted into the vascular access for dialysis and no blood is removed from the subject for this measurement. The first measurement will be done within 2 weeks of starting hemodialysis and a second measurement will be obtained approximately 2 weeks later. Thereafter, the access blood flow measurements will be done monthly until the end of your participation in the study. This information will be recorded as part of the study and also available to your physician and other dialysis providers. If the vascular access

blood flow meets established criteria indicating a high risk of significant narrowing then you will be referred for an angiogram of the access to determine the severity of the narrowing and whether balloon angioplasty is indicated.

Once a month, during the time you are in the study a member of the research staff will interview and examine you to determine whether there have been any problems with your vascular access graft or the study medication. The research staff will record the medications and dosages that you are taking and will assess your compliance with taking the study medication. At this time the research staff will also review your medical records and routine lab results from your dialysis unit or renal clinic. Any hospitalization, access-related procedure, episode of bleeding or other significant medical event thought to be related to the study medication will be recorded. If at any time the study team feels that the drug therapy is causing a side effect, the medication may be stopped and the standard care for patients on hemodialysis with arteriovenous grafts will be offered. Each monthly study visit will take about 30 minutes and this generally will occur when you are on dialysis or come to clinic for your regular evaluations. However, if you have not started on dialysis within 1 month after having the new access placed, then special arrangements will need to be made with the research study coordinator for a monthly evaluation until you start on dialysis.

Every three months during the time you are on the study the study coordinator or study physician will conduct a Quality of Life Questionnaire. This will consist of 3 questions about how you have been feeling since your graft was created. You are free to skip any questions that you do not wish to answer.

Your participation in the study will end one month after the first failure of your new vascular access graft or when the study ends, whichever comes first. A vascular access failure means the access has clotted or a procedure such as angioplasty is performed to prevent graft failure. If your access fails, then procedures will be performed to restore its function as described above. Once your participation in the study ends you will continue to receive the standard of care for all patients on hemodialysis provided by your regular dialysis physician. The study is currently projected to take up to 4 years, however, for most subjects their participation will last about 1 year.

A panel of experts called the Data Safety and Monitoring Board will monitor the results of the study. If the Board determines that there have been too many complications in the study or that the results of the study are determined, they will recommend that the study be stopped. This Board offers important protection to you as you participate in this research.

MEDICATION UNDER INVESTIGATION: Aggrenox is an FDA-approved medication for the prevention of stroke in patients who have had a prior stroke or near stroke. The components of Aggrenox, aspirin and dipyridamole have been used individually and in combination to prevent arterial clotting that leads to a heart attack or stroke. Even though both of these medicines have been used in many patients, the combination medication Aggrenox has not yet been approved for prevention of clotting in arteriovenous vascular access grafts.

POSSIBLE RISKS:
The possible risks associated with participating in this research are as follows.

Aggrenox. This medication may help your medical problem but also cause side effects. The two active medications in Aggrenox, dipyridamole and aspirin, are widely used and have well-characterized side effects and risks, including an increased risk of bleeding, gastrointestinal disturbances and headache. However, it is not possible to predict whether you will experience some or none of these side effects. Information about the possible side effects of treatment with Aggrenox is based upon the experiences of the men and women who have taken this medication in the past.

Side effects usually stop when treatment with Aggrenox stops. However, there is a possibility that some side effects may remain for a long time or develop after stopping treatment.

Increase in risk of bleeding. Dipyridamole is a weak blood-thinning medicine, but several studies show that it does not significantly increase the risk of bleeding over aspirin alone. In one large study of more that 6,000 patients without kidney failure, bleeding occurred in 3.6% of patients on Aggrenox compared to 3.2% on aspirin alone, 1.5% on dipyridamole alone and 1.3% on placebo. The overall risk of bleeding may be higher in patients with kidney failure. One study reported that bleeding occurred in 5% of dialysis patients on placebo and 8.4% of dialysis patients on Aggrenox. No patients were reported to have died from bleeding and the overall survival rate for subjects on Aggrenox was better than for those on placebo. These studies suggest that Aggrenox is likely to be safe and reasonably well tolerated. We anticipate that the risk of bleeding with Aggrenox will be increased when it is used in combination with other blood thinning medications, such as coumadin or anti-inflammatory medicines, such as Motrin (ibuprofen). If you require any of these types of medications during the course of the study, the research team will discontinue the study capsules. You may take aspirin if your physician has recommended this. Tylenol is also okay to take for headaches, fever and pain when you are on Aggrenox.

Allergy to aspirin. If you have an allergy to aspirin other non-steroidal medications such as Motrin or dipyridamole you should not take Aggrenox. Aspirin allergy is sometimes seen in patients who have the combination of asthma, sinus congestion and nasal polyps. If you have this combination of symptoms you should not participate in the study.

Gastrointestinal side effects. Aggrenox can exacerbate peptide ulcer disease. If you have active peptic ulcer disease you may not participate in this study. Other side effects of Aggrenox that can occur include abdominal discomfort, heartburn, nausea or vomiting.

Other possible side effects. Other side effects, including headache, dizziness and angina have been reported to occur in some subjects taking Aggrenox.

Risks to an unborn child or a breast-fed infant. It is not known whether Aggrenox may harm an embryo or fetus or an infant who is breast-feeding. It is not known whether treatment with Aggrenox may lead to birth defects.

Women: A woman who is pregnant or is breast-feeding an infant may not participate in this research. A pregnancy test will be performed for any woman who is capable of bearing a child and wishes to participate in this study. A pregnancy test may be repeated later during the study for safety. If you are a woman who can bear children and suspect pregnancy during the time you receive treatment in this study, please notify the study staff immediately. Your participation in this research will stop. The study staff can discuss new care with you.

Avoiding pregnancy: Pregnancy should be avoided while you receive medications in this study. It is your responsibility to discuss with the study team the appropriate ways to avoid pregnancy. If your method of avoiding pregnancy changes while you receive treatment in this study, it is your responsibility to inform the study team as soon as possible. Your participation in this research may stop, and your study physician can discuss new care with you.

Placebo. If you receive a placebo, you will not receive active medication for your condition. If your condition becomes worse, your participation in the study may stop. If this happens, your doctor can discuss alternative care with you.

Blood samples. You may experience discomfort, bleeding, and/or bruising. You may feel dizzy or faint. On a rare occasion, an infection may develop at the site where the blood was collected.

Unforeseen risks. A previously unknown side effect may occur. A side effect because of an interaction of Aggrenox with other medications you take (prescribed or over-the-counter) may result from your participation in the study. It is not possible to estimate the chances of such occurrences or their severity.

How you can help reduce some of the risks. During your participation in this study, research personnel will watch closely to determine whether there are complications that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep appointments.
- Follow the doctor's recommendations. Tell the doctor about all prescription, non-prescription and herbal medications that you are taking.
- Let us know if your telephone number changes.
- Store study pills in a secure place at home away from anyone who is unable to read and understand labels, especially children.
- Tell your study doctor before taking any new prescription, non-prescription or herbal medication even if the medication is prescribed by another doctor for a different medical problem.
- Tell your regular doctor about your participation in this study.

What to do if you have problems. If you experience unusual symptoms or pain at any time during your participation in the study, the study staff can recommend treatment. Please report the problem to the study staff promptly. *Telephone numbers where they may be reached are listed on page 1 of this consent form.*

POSSIBLE BENEFITS: There may be no personal benefit for participating in this study. In the future, other people on hemodialysis may benefit from the results of this research. New information may lead to improved medical care.

ALTERNATIVES TO PARTICIPATION IN RESEARCH: Before deciding whether to participate in this study, your doctor will have discussed the other options that are available to you. Rather than participating in this study, the alternative is to have the usual care given to patients that get a synthetic vascular access graft for hemodialysis. While Aggrenox is available by prescription to patients who do not participate in the study, it is not currently FDA approved for this indication. The usual care does not currently involve giving Aggrenox or any other similar medication after surgery. At this time, the usual care for a clotted or failing graft is to modify the existing graft if possible, or perform a new surgery to place either a new access or a catheter for dialysis. If you decide to participate in this research, but later change your mind, you may receive the alternative care.

THE DOCTOR'S DECISION TO STOP YOUR PARTICIPATION: Under certain circumstances, your participation in this research study may be ended without your consent. This might happen because:

- Your doctor believes that participation in the study is not safe for you.
- You are placed on a blood thinning medication, such as coumadin, or must take a non-steroidal antiinflammatory medication such as Motrin (ibuprofen).
- The sponsor or the Food and Drug Administration (FDA) stops the research for safety.
- The sponsor cancels the study.
- You fail to keep appointments and to follow the study procedures and your doctor's recommendations.

PROCEDURES AFTER STOPPING PARTICIPATION IN THE STUDY: If you, the doctor, or the sponsor stops your participation in this research, it is your responsibility to come to the clinic for evaluations and discussion about future treatment. At that time, please return any unused study medication, including empty containers.

COSTS: You will not be charged for study medication, study-related blood work, or study visits. Expenses related to angiograms, angioplasty, and procedures to open a clotted graft are your responsibility or the responsibility of your insurance provider. Because these procedures are standard practice in the medical community they are typically covered by insurance providers. [Each center should specify whether parking expenses will be paid.] There are no funds available to pay for transportation to and from the clinic, lost time away from work and other activities, lost wages, or child care expenses.

PAYMENTS TO PARTICIPATE: You will receive no payment to participate in this study.

VOLUNTARY PARTICIPATION: You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to discontinue participation in the research at any time. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you will receive at this center. Any significant new information that

becomes available during your participation in the research and may affect your health, safety, or willingness to continue in the study will be given to you.

CONFIDENTIALITY: You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law. The investigators will release such private information only to the sponsor. Representatives of the FDA, other U.S. and foreign government agencies, and the sponsor may review and photocopy your medical and research records to assure the quality of the information used in the research. The results of this research may appear in scientific publications without identifying you by name.

We need to record all of your hospitalizations and other important medical events that take place while you are in the study and for five years after the end of the study. For this reason we will ask to record your Social Security number. Your Social Security number will be kept secure. You may refuse to give your Social Security number and still participate in the study.

An Institutional Review Board (IRB) is a group of people who are responsible for assuring the community that the rights of participants in research are respected. Members and staff of the IRB at this medical center may review the records of your participation in this research. A representative of the Board may contact you for information about your experience with this research. If you wish, you may refuse to answer any questions the representative of the Board may ask.

The medical and research information recorded about you will be used within [institutions] and/or disclosed outside [institution] as part of this research. Some of the tests and procedures done solely for this research study also may be placed in your medical record so your other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in the medical chart.

Your access to research information about you will be limited while the study is in progress. Preventing this access during the study keeps the knowledge of study results from affecting the reliability of the study. This information will be available should an emergency arise that would require your treating physician to know this information to treat you best.

Your research information may be disclosed to _____, the research study Sponsor and its agents, the [institutions] research review staff, the U.S. Food and Drug Administration, and other outside collaborators or laboratories that are participating in this study, if any that are listed as follows:_____. The [institution] also may use and disclose this information for treatment and payment reasons. The [institution] must comply with legal requirements that mandate disclosure in unusual situations. Otherwise, the information recorded about you as part of this research will be maintained in a confidential manner. It is possible that information disclosed about you outside the [institution] could be re-disclosed and no longer protected by federal privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to _____, at [institution and address]. If you do so, any information previously disclosed cannot be withdrawn. The [institution] will not use or disclose the information collected in this study for another research purpose without your written permission, unless the [institution] Institutional Review Board gives permission after ensuring that

appropriate privacy safeguards are in place. The Institutional Review Board is a committee whose job is to protect the safety and privacy of research subjects.

COMPENSATION FOR INJURY:

- In the event of research related injury, medical treatment is available at [*your institution*].
- No compensation for treatment of research-related injury is available from [*your institution*] unless the injury is proven to be the direct result of negligence by an employee of [*your institution*].
- Should a research-related injury occur, you and/or your medical or hospital insurance carrier must pay for the cost of the treatment.

YOUR QUESTIONS: Questions are encouraged. The study staff is available to answer your questions about this research. The Chairman of the IRB is available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research. You may telephone the Chairman of the IRB during regular office hours at [*telephone number*].

YOU WILL HAVE A COPY OF THIS SIGNED AND DATED CONSENT FORM TO KEEP.

Your signature indicates that you have read (or been read) the information provided above, that you have received answers to all of your questions, and that you have freely decided to participate in this research. By agreeing to participate in this research, you are not giving up any of your legal rights.

_____ Participant's name (printed) and signature (if at least ten years of age)	_____ Date
_____ Legally responsible representative's name (printed), signature, and relationship to the participant	_____ Date
_____ Name (printed) and signature of person obtaining consent	_____ Date
_____ Witness'/translator's name (printed) and signature	_____ Date

Please indicate below whether or not you agree to let us record your Social Security number. The Social Security number will be used to obtain access to Medicare and other health databases in order to obtain information about your important medical events while you are in the study and for up to five years after the study ends. Your Social Security number will be kept secure. You may take part in this study regardless of whether you permit your Social Security number to be collected. You may withdraw your consent for continued use of your Social Security number at any time.

Do you agree to allow the study team to collect your Social Security number?

o Yes, the study team may collect my Social Security number. _____ (initials)

o No, the study team may not collect my Social Security number. _____ (initials)

Your signature below indicates that you agree, in addition, to let us record your Social Security number.

_____ Participant's name (printed) and signature	_____ Date
_____ Legally responsible representative's name (printed), signature, and relationship to the participant	_____ Date
_____ Name (printed) and signature of person obtaining consent	_____ Date
_____ Witness'/translator's name (printed) and signature	_____ Date

YOU WILL HAVE A COPY OF THIS SIGNED AND DATED CONSENT FORM TO KEEP.

2.8.2.3 Exclusion criteria

Exclusion criteria are established to exclude subjects who might be at excessive risk from participation, those who are unlikely to comply and unusual subjects who might introduce bias in the results if they were randomized unequally between study groups. Note that patients who have a medical need for aspirin will not be excluded from participation in this study.

The exclusion criteria are as follows:

Women must not be pregnant, breast feeding, or plan to be pregnant during the course of the study.
Rationale – Aggrenox should not be used in pregnancy and is listed as a category C/D medication by the FDA. This is primarily due to the presence of aspirin and the concern that this can lead to fetal hemorrhage. Aspirin is also considered unsafe for breastfeeding mothers. Therefore, women who participate must not be pregnant, breastfeeding or plan to get pregnant during the study, If they are capable of having a child, they must be practicing an effective form of birth control.
Method of assessment – All women under the age of 50 who have not passed menopause (surgical or biological) will be considered capable of bearing children. Any woman who is potentially capable of

bearing children will be asked if they might be pregnant or plan to become pregnant or are breastfeeding and wish to continue breastfeeding. A pregnancy test will be performed on any woman who has neither been amenorrheic for the previous 12 months nor surgically sterilized and who is sexually active and not using an acceptable means of birth control.

The presence of ongoing bleeding.
Rationale – Aggrenox has aspirin and dipyridamole that inhibit platelet function and might exacerbate bleeding. This exclusion is to lower the risk of potential adverse side effects for the patient.
Method of assessment – The potential subject and their physician will be asked about whether they have knowledge of any ongoing bleeding and the person's medical records will be reviewed for any evidence of current or ongoing problems with bleeding in the last 3 months. A recent blood transfusion within the last 3 months may be evidence for possible recent bleeding and this will be discussed with the subject's primary care physician before enrolling such a patient.

The presence of a known bleeding disorder (e.g., hemophilia or von Willebrand's disease).
Rationale - Aggrenox has aspirin and dipyridamole that inhibit platelet function and might exacerbate bleeding. The risk of a major or life-threatening bleed would be higher in people who have an underlying bleeding disorder such as hemophilia or von Willebrand's disease.
Method of assessment – The potential subject and their physician will be asked about whether they have knowledge of any bleeding disorder and the person's medical records will be reviewed for any history of a known bleeding disorder. If there is a question about whether a medical condition would pose a serious risk of bleeding this will be discussed with the primary care physician and the Principal Investigator at the study site.

Recent bleeding episode requiring transfusion within 12 weeks of entry.
Rationale - Aggrenox has aspirin and dipyridamole that inhibit platelet function and might exacerbate bleeding. This exclusion is to lower the risk of potential adverse side effects for the patient.
Method of assessment – The potential subject and their physician will be asked about whether they have knowledge of any episode of bleeding that required a transfusion within the previous 12 weeks. The person's medical records will also be reviewed for any history of bleeding within the last 12 weeks that required a blood transfusion.

The presence of acute ulcer disease.

a. Rationale – The aspirin contained in Aggrenox can irritate the lining of the gastrointestinal tract and exacerbate gastrointestinal ulcers. This would predispose the person to an excessive risk of bleeding or intestinal perforation.
b. Method of assessment - Acute ulcer disease is defined as a new diagnosis of peptic disease including esophagitis, gastritis, or ulcer or the initiation of treatment for acute ulcer disease with proton pump inhibitors, H2 blockers or therapy for Helicobacter pylori within three months prior to obtaining consent. This will be determined by asking the patient and their physician whether the potential subject has had recent problems with stomach or intestinal ulcers or have started on a medication for ulcers or Helicobacter pylori within the last 3 months. The person's medical records will also be reviewed for evidence of any of these exclusion criteria.

Known allergy or adverse reaction to Aggrenox or any of its study components.

a. Rationale – This exclusion criterion is to avoid preventable adverse reactions in people who have a known allergy or prior adverse reaction to Aggrenox or either of its study components (dipyridamole and aspirin).
b. Method of assessment – Ask the potential subject about any prior history of allergy or adverse reaction to Aggrenox or either of its components (aspirin or dipyridamole) and consult their medical records for evidence of any allergies.

Required use of warfarin, dipyridamole, non-steroidal anti-inflammatory drugs or other antiplatelet agents other than aspirin.

Rationale – Use of other anticoagulants and antiplatelet agents increases the likelihood of a serious bleed when combined with the study medication, Aggrenox. Use of aspirin is not an exclusion criterion because the study medication Aggrenox has a low dose of aspirin and addition of extra aspirin will not substantially increase the risk of bleeding.

Method of assessment - The potential subject and their physician will be asked whether the subject is on any of the proscribed medications. It is important to ask the potential subject about over-the-counter medications they may be taking. The person's medical records will also be reviewed for a history of being on any of these medications. A list of commonly used anticoagulants, antiplatelet agents and non-steroidal medications is shown in Table 1. Since the list might not be complete and new medications can come on the market, if the potential subject is on any unknown medications then the study personnel should consult their local pharmacist or an up to date drug reference such as Micromedix for questions about an unknown medicine. Any remaining questions regarding this issue should be discussed with the person's primary care physician and the Principal Investigator at the study site.

Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg.

Rationale – Use of the study medication, Aggrenox in the setting of uncontrolled severe hypertension may increase the risk for a hemorrhagic stroke, so these subjects can not be enrolled until their blood pressure is better controlled.

Method of assessment – The blood pressure measurement should be taken from the arm using the brachial artery after the person has been seated quietly for 5 minutes. It can be done using either a mercury or aneroid sphygmomanometer or an automated blood pressure cuff. If the blood pressure is done in a person on dialysis then the pre-dialysis sitting blood pressure should be used.

Time of assessment - The blood pressure measurement should be obtained at the time of the screening evaluation. If the blood pressure was not ascertained at the time of the screening evaluation, then the most recent blood pressure measurement can be used as long as it was done no more than 45 days prior to the time of the screening evaluation.

Who does the measurement – The measurement can be done by any medical personnel in the clinic or dialysis unit who are trained and qualified to perform blood pressure measurements using the available equipment. The blood pressure should be recorded in the person's medical record as well as on DAC study form 311. Study personnel may do the blood pressure measurement if they are qualified to do so using the available equipment. If a recent blood pressure measurement has not been done in clinic and the potential participant does home blood pressure monitoring on a regular basis (at least twice a month) then the home blood pressure record can be used. The study coordinator should review the person's blood pressure measurements over the last 2 months (at least 3 measurements) to determine whether they are under 200 mmHg systolic and 115 mmHg diastolic. Then record the most recent measurement and the date on DAC study form 311.

What to do if the potential subject has severe hypertension – If a person has a blood pressure more than 160 mmHg systolic or 100 mmHg diastolic and they are not known to have documented "white coat hypertension" then they should be told that their blood pressure is high and they should consult with their nephrologist or primary care physician. If the blood pressure is more than 200 mmHg systolic or 115 mmHg diastolic then the person's primary care physician should be contacted directly and arrangements made for expeditious follow-up and management of the severe high blood pressure. If the blood pressure is this high and the person is having symptoms such as chest pain, neurologic symptoms or headaches then the person should be referred for immediate evaluation by their primary physician or the emergency room.
"White coat" hypertension – Some people have documented clinic blood pressure measurements that are quite high while their home blood pressure measurements are near normal. If a potential participant has a clinic blood pressure that exceeds the limits but are known to have ambulatory blood pressure measurements that are better controlled (e.g. less than 160 systolic and 90 diastolic) then they may be enrolled if their primary physician and the principal investigator at the study site agree to the enrollment.

Baseline platelet count less than 75,000/mm^3.
Rationale – A low platelet count may increase the risk for serious bleeding for a study participant on Aggrenox.
Method of assessment – A complete blood count (CBC) will be drawn at the time of the preoperative evaluation just prior to the scheduled access surgery to determine the person's platelet count.
Who will perform the phlebotomy – Clinic staff or a phlebotomist at the study site.
Where will the blood be analyzed – At the local laboratory as part of the person's presurgical evaluation.
When must this be done – The platelet count must be done within 45 days of randomization.

Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.
Rationale – The presence of any of these manifestations of severe or active liver disease may increase the risk for serious bleeding for a study participant on Aggrenox.
Method of assessment – The study personnel will ask the potential participant whether they have had recent problems with liver disease including yellow eyes, swelling up with fluid in their abdomen or any problem with bleeding including vomiting or coughing up blood or having blood in their stool. The study personnel will look at the potential participant's eyes to see if they are yellow. The study personnel will review the potential participant's medical records and contact their primary physician to determine whether there is any current concern about decompensated cirrhosis or hepatitis as documented by the presence of jaundice, ascites, or bleeding varices.
Who will perform the evaluation – The study coordinator or study investigator.
When must this be done – This evaluation must have been done within 45 days of randomization.

Current problem with substance abuse.
Rationale – Problems with substance abuse are likely to lead to non-compliance with the study protocol and possibly expose the person to excessive risk for complications from taking the study medication, Aggrenox.
Method of assessment – Substance abuse will be defined as known and ongoing use of illegal substances or excessive and recurrent use of alcohol that might be expected to frequently impair the person's judgement or expose the person to increased risk of bleeding. This will be based on the best judgement of the study coordinator and principal investigator at the site after talking with the potential participant and their personal physician and reviewing the person's medical records. To

elicit the information from the potential subject the study coordinator should first explain the concern about using illicit substances or excessive alcohol while enrolled in the study. Then the study coordinator should ask the person whether they use illicit drugs and if so what types of substances and by what route and how often. If the person uses alcohol, the coordinator should determine how much alcohol is consumed and whether the person has had recent problems attributable to alcohol abuse such as a hospitalization, an alcohol withdrawal seizure, or an arrest for driving under the influence of alcohol.

Concurrent participation in another medical intervention trial.
Rationale – Participation in more than one intervention trial raises the possibility of possible unknown medication interactions leading to adverse events or possibly influencing the outcome of the current trial. In addition, conflicts between the study design of the two trials may arise that might lead to the subject having to drop-out prematurely.
Methods of assessment – The potential subject will be asked whether they are currently participating or plan to participate within the next 12 months in another research trial. If the person is currently participating or plans to participate in a trial but the nature of the trial is not certain, then the principal investigator at the study site should contact the principal investigator for the other trial to determine whether the other trial involves an intervention (as opposed to being an observational trial) and whether any other conflicts would arise between the two trial designs.

Anticipated non-compliance with medical care based on physician judgment.
Rationale – Non-compliance will adversely impact the outcome of the trial and potentially place the participant at increased risk for an adverse event.
Methods of assessment – This is based on the best judgement of the study coordinator and study investigator after talking with the potential participant and their personal physician as well as reviewing their medical records. A regular history of missing scheduled appointments or not taking prescribed medications will be taken as evidence for non-compliance.

Patient refusal.
Rationale – This is self-explanatory. A person must consent to participate to be enrolled in the study.
Methods of assessment – If the subject states that they no longer wish to be involved in the study or by their actions indicate a lack of willingness to proceed with the study then they will be excluded from the study.

2.8.3 Baseline data

2.8.3.1 Purpose

Baseline data is collected at the time of enrollment to record demographic, clinical and laboratory data that may predict a participant's risk of developing access failure or their risk for a complication from the study medication. This information will be used to confirm that randomization led to equal distribution of potential risk factors for access stenosis between the two groups. It will also be used in subsequent statistical analyses to determine what factors were actually predictive of the risk for access failure in the study population and whether there were subgroups of subjects who were more or less responsive to the therapeutic intervention.

2.8.3.2 Obtaining the baseline data

Baseline data will be obtained by the study coordinator or study investigator by interviewing the potential participant, talking with their primary physician and reviewing their medical records. The data will be obtained at the time of enrollment as described in sections 2.3-2.5 above.

2.8.3.3 Recording the baseline data

Baseline data is recorded on DAC study forms 322, 324, 331, 333, 341, and 351 (See Table 1). Baseline data to be recorded includes:

1. Patient identification –
   a. Rationale – Self explanatory.
   b. Information to be collected – Name, date of birth, gender and race.

2. Patient's contact information –
   a. Rationale – Contact information must be available for each subject to allow them to be contacted if necessary for scheduling appointments, follow-up, providing study medications, and for rapid notification if any concerns regarding the study should arise.
   b. Information to be collected – Current home mailing address, work and home telephone numbers, FAX number (if applicable), e-mail (if applicable), best time and method to reach them, any alternate contact information (family member, relative or close friend). This information will not be recorded on any forms.
   c. Source of information – The potential participant and the medical records.

3. Date of enrollment – Automatically recorded as date that screening data is entered.

4. Kidney disease history –
   a. Rationale – The cause of kidney disease (e.g. diabetes) and the length of time on dialysis may be risk factors for access failure. [Knowing if the person had a renal transplant(s) and how long the transplant(s) lasted will allow calculation of actual years of dialysis therapy after developing ESRD.]
   b. Information to be collected –
      i. Cause of ESRD – Categorize as one of the following: diabetes, hypertension, polycystic kidney disease, glomerulonephritis, interstitial nephritis, hereditary nephritis, urinary tract disease (including obstruction), solitary kidney, ischemic nephropathy, acute renal failure, unknown with either > 3 g proteinuria/day, 1-3 g proteinuria/day or < 1 g proteinuria/day, other or unknown.
      ii. Date of ESRD – date when person was first started on chronic dialysis or had first renal transplant. If subject is pre-dialysis this will be left blank and filled in later when they start.
      iii. Start date for hemodialysis – date of first regular hemodialysis session for ESRD. (Not date of dialysis for acute renal failure). This may be the same as the date of ESRD.
      iv. Transplant – Whether the patient is on a transplant waiting list.
      c. Sources of information – The potential participant and the medical records. If a person has had a renal transplant or is already on dialysis the cause of renal failure and date of first renal transplant or regular dialysis will be found on the ESRD Medical Evidence Report (HCFA 2728).

5. Vascular access history –
   a. Rationale – It is important to have an accurate vascular access history because the number, type and location of prior accesses may be an important covariate in determining the risk of repeat access failure or response to study medication.
   b. Information to be collected

i. Number of prior arteriovenous access sites used
- Current type of access attempted - fistula, graft, internal jugular, subclavian, femoral, subcutaneous port other, or unknown
- Location - left or right side; forearm, arm, leg or other

c. Sources of information – Ask the potential participant and review the medical records to obtain the access history. If the potential participant came from another dialysis unit it may be necessary to contact that unit to obtain this information. The arms of the potential participant will be inspected for scars looking for evidence of prior access surgeries in distinctly different locations. The potential participant should be asked about each scar. If they are unable to explain the origin of the scar then the medical records will need to be reviewed to determine what surgery was performed. If an access database is available then this should also be consulted to determine the potential participant's prior access history. Questions about the interpretation of the number, type or location of any prior accesses will be addressed by the principal investigator after consulting the medical records and if necessary talking with the potential patient's nephrologist and access surgeon.

6. Central catheter history –

a. Rationale – Having a central catheter is a risk factor for developing central stenosis which may predispose to an increased risk of access failure.

b. Information to be collected –
i. Is there a current central catheter – yes/no
ii. If so, record whether the current catheter is:
- Temporary or permanent (i.e. a tunneled catheter)
- Subclavian or internal jugular vein
- What side (right or left)
iii. If no current catheter, has the subject ever had any central catheter placements – yes/no;
If yes, where was it located - right, left or both

c. Source of information – The potential participant will be asked if they currently have a catheter or have ever had a previous catheter for the purpose of hemodialysis. If they have a current catheter, note the location of the catheter, whether it is tunneled and try to determine when it was placed. If they have had a previous catheter, then determine the location of the catheter(s). The subject's neck and upper chest will be examined for a current central catheter. If there is no catheter, but surgical scars are apparent then ask the subject whether any of the scars were for a catheter. If an access database is available then that may be a useful source of information on prior catheter placements. If there is uncertainty, the dialysis records should be reviewed. At many centers, the dialysis records record the type access used for hemodialysis.

7. Past medical history –

a. Rationale – The subject's past medical history will be recorded looking for evidence of vascular disease that may be a risk factor for access failure and evidence of any problems that would predispose to hemorrhage.

b. Information to be collected –
i. Diabetes
- If yes, record the treatment being used for the diabetes.
ii. Vascular disease – record any of the following that have occurred or are currently present: myocardial infarction, coronary artery bypass graft, congestive heart failure,

stroke, transient ischemic attacks, peripheral vascular disease, a history of a peripheral artery bypass graft, amputation for any reason other than trauma.

iii. Hyperlipidemia – Any of the following meet the criteria for hyperlipidemia:
A diagnosis of hyperlipidemia or hypercholesterolemia or
taking a cholesterol or lipid lowering medication (e.g. atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, gemfibrozil, niacin, cholestyramine, colestipol, etc.) or
Total cholesterol of greater than or equal to 240 mg/dl or an LDL cholesterol greater than or equal to 160 mg/dl.

iv. Bleeding disorder or coagulopathy – a subject carrying a diagnosis of hemophilia or von Willebrand disease or current thrombocytopenia of any cause (see biochemical tests below).

Source of information – Ask the potential participant about whether they have had any of these diagnoses and where applicable the year of diagnosis. A history sheet can be made up for the subject to fill out and give to the study coordinator to assist with obtaining this information. The past history section in the potential participant's medical records will be reviewed looking for the presence of any of these diagnoses.

List of current medications –

a. Rationale – Certain medications may affect the rate of access failure (e.g. angiotensin converting enzyme inhibitors, fish oil, statins, erythropoietin etc.). In addition, the combined use of an anticoagulant or antiplatelet agent while on the study medication is prohibited due to increased risk of bleeding. The dose of aspirin that a participant is on may be a confounding factor and will be recorded.

b. Information to be collected – A complete list of medications, including prescription medications, any over-the-counter medications, vitamins and herbal medicines that the person is taking at the time of the enrollment. With the exception of aspirin, the medication dosage does not need to be recorded. For aspirin, the prescribed dose of aspirin will be recorded. The dosage of aspirin taken in combination over-the-counter medications will not be estimated but the drug will be listed as a medication. All insulin is coded as humulin, NDC code 00002951501.

c. Source of information – Ask the potential participant about what medications they are currently taking. By far, the best way to assess this is by having the potential participant bring all their pill bottles including any over-the-counter medications, vitamins or herbal products to clinic. Alternatively, if the subject has an up to date list of medicines then that can be used to get the list of medicines. If the potential participant does not bring the pill bottles or have a current list of medicines or there are questions about the accuracy of the list then the study coordinator may need to contact the person at home to have participant or their caregiver read off all their medications. If a person gets all their medications from a single pharmacy then that can be another means to get this information but it is less reliable. Reviewing a recent clinic visit or discharge summary in the medical records can help to confirm the medication list but is not always accurate. Remember that people on dialysis may get medications (e.g. erythropoietin, intravenous iron or vitamin D analogs) only at dialysis and these medications may not show up on any other records. The study coordinator will need to contact the dialysis unit or review the dialysis unit medication records to determine if the subject is getting any of these other medicines.

Tobacco use -

a. Rationale – Use of tobacco is a risk factor for vascular disease and may influence the risk of vascular access failure.
b. Information to be collected –
    i. Did the person ever smoke?
    ii. If yes, then record the total number of years they smoked?
    iii. How many packs of cigarettes per day did they smoke?
    iv. Are they currently smoking?
    v. If not currently smoking, record the number of months since they stopped.
c. Source of information – This information should come from asking the potential participant about their smoking history.

Quality of life questionnaire –

a. Rationale – Vascular access failure can be an important source of concern for people on dialysis and could affect their quality of life.
b. Information to be collected – The three questions listed on the quality of life questionnaire
c. Source of information – The potential participant is asked to provide answers to the three questions and those answers are recorded on the form.

Blood pressure. See screening data.

a. Rationale – Blood pressure is an important determinant of the development and progression of arterial vascular disease. It might be an important factor in determining the risk of vascular access failure. Excessive elevations in blood pressure over 200 mmHg systolic and 115 mmHg diastolic may increase the risk for intracerebral hemorrhage while on the study medication and would exclude a potential participant from participation in this study.
b. Method of assessment – see screening data.
c. Time of assessment - see screening data.
    Who does the measurement – see screening data.

12. Height and weight

a. Rationale – This information is needed to calculate body mass index (BMI) and a post-dialysis weight is needed to calculate kT/V as a measure of adequacy of dialysis.
b. Information to be collected – Height measured in centimeters and weight measured in kilograms.
    Method of assessment – Height and weight should be measured with the patient standing without shoes at the time of the screening or enrollment visit prior to randomization. If the person is on dialysis then the post-dialysis "dry" weight should be recorded. If the person can not stand (e.g. wheelchair bound) or there is no means to measure height then this should be noted and the estimated height recorded. If a weight can not be recorded in clinic on a wheel-chair bound person then the most recent weight available for the person will be used. The date that the height and weight were done or estimated should be recorded.

13. Periodontal disease

a. Rationale – Peridontal disease is a common inflammatory state that can elevate the C reactive protein (CRP) and has been proposed as a risk factor for vascular access failure.
b. Information to be collected – The presence or absence of significant periodontal disease and whether the person is edentulous.

c. Method of assessment – Ask to look into the person's mouth using a flashlight. Check the upper and lower teeth and gums looking for any large cavities in the teeth or severely inflamed gums. If the teeth and gums look reasonably healthy then score it as no periodontal disease. If there are any large cavities or active gum disease then peridontal disease is present. If no teeth are present (or the person has both upper and lower dentures without any native teeth present) then the person is edentulous.

14. Baseline biochemical measurements

a. Rationale – Coagulation test (platelet count) is needed at baseline to exclude people who would be at increased risk of bleeding on Aggrenox. The hemoglobin is measured at baseline to assist with monitoring for significant future bleeding on study medication. The serum albumin has been shown to inversely correlate with the risk of access failure.

b. Information to be collected –
   i. Coagulation studies (see screening section) – platelet count
   ii. Hemoglobin
   iii. Hematocrit
   iv. Serum albumin

c. Source of information – These blood tests will be obtained at the local study site as preoperative laboratory tests and in the routine management of patients with ESRD. The tests must be done within 45 days of randomization.

d. Funding for local lab tests - If they are not ordered as part of the routine presurgical laboratory tests or the routine management of the ESRD patient then they may have to be paid for out of the study budget at the local site.

2.8.3.4 Collecting specimen for DNA and blood repository

Rationale

The DAC Study will be the largest and most comprehensive prospective interventional study to date of access failure. As such, it provides a unique opportunity to study biological factors that correlate with access failure and the response to therapy. Examples of such epidemiological studies that have been proposed include: 1) a genetic association study looking at whether single nucleotide polymorphisms in known cardiovascular candidate genes are associated with the risk of access failure and 2) a study of the correlation between serum factors linked to cardiovascular risk in other vascular beds (e.g. asymmetrical dimethylarginine, advanced glycation end products, C-reactive protein, lipoproteins, and homocysteine to name a few) and access failure. The original NIH award did not provide for funds to perform these important epidemiological studies as it was expected that these ancillary studies would be submitted as independent investigator-initiated grant proposals and subject to the standard peer review process to determine funding priority. However, if tissue samples including blood and DNA are not obtained and stored during the study then these future epidemiological studies will be impossible to perform. This is particularly true for serum markers which should optimally be drawn prior to access placement. While DNA samples for genotyping experiments theoretically can be obtained at any time during the study, as time goes by some people will be lost to follow-up and more importantly the high mortality rate for people on dialysis (17-22% per year) raises the potential risk of informative censoring. Therefore it is important to obtain blood throughout the study to prepare and store DNA and serum for future epidemiological studies.

Procedures for specimen collection and storage

Specimen collection. At the time of enrollment all subjects will be informed about the opportunity to participate in this additional study in which a sample of their blood and DNA will be removed and stored to look for factors associated with the primary and secondary outcomes. Subjects will be informed that they have the opportunity to participate in the primary drug intervention trial without participating in these additional studies involving storage of their blood or DNA. In addition, they will have the opportunity to selectively participate in either the blood (serum) storage or DNA storage or both studies. Due to limited resources, subjects will not be allowed at this time to participate in the blood or DNA studies without participating in the primary drug intervention trial. The informed consent document will provide the opportunity for subjects to selectively indicate their willingness to allow storage of their blood (serum) and/or DNA for these studies. Subjects will be informed that their specimens will also be available to other qualified investigators studying other research questions of importance to people with kidney disease.

Subjects who were enrolled and randomized into the primary drug intervention study prior to initiation of the blood and DNA storage will also be offered the opportunity to participate in this additional study.

If the subject agrees to participate and signs the informed consent then about 30 ml of venous blood will be withdrawn into the appropriate containers for preparation of serum and DNA. The samples will be labeled with the subject's study code and the date and then placed into a shipping container and shipped at room temperature to the central processing and storage facilities.

Central DNA and blood repositories (See Section 2.8.3.4), Detailed Procedures for Shipping Specimens). Samples will be processed and stored at central repositories under contract with NIDDK. There will be one repository that prepares and stores the DNA samples. This repository will also prepare plasma for storage at a second repository that will also process blood to obtain serum for storage.

Confidentiality of the samples will be maintained by labeling the specimens with the subject's study code but no personal identifying information. The central processing and storage repositories will use their own identification code to label and store the samples. The DAC Study DCC database will include a link between the original study number and the central repository identification codes. The only site where the study code is directly linked to personal identifying information is at the clinical center where the person was enrolled.

Access to specimens for approved studies

Access to the specimens will be provided to all qualified investigators with the necessary funding and an approved study protocol to investigate problems relevant to people with kidney disease. The mechanism for obtaining approval to analyze specimens stored in the repositories is outlined in the Ancillary Studies section of the DAC Administrative Manual of Operations. Upon approval from the DAC Steering Committee the DCC will notify the appropriate repository to provide the specified samples labeled with the central repository ID code to the qualified investigator's lab for analysis. Subsequent data analysis linking the ancillary studies laboratory data to the original dataset will be done in coordination with the DCC where the master key code is maintained.

Risks
Obtaining a blood sample may entail momentary pain and a risk of bleeding at the time of phlebotomy and the possibility of subsequent bruising. The major risk of the blood and DNA repository is that a breach of patient confidentiality could occur and the results of laboratory studies, particularly the results of DNA genotyping might get linked to personal identifying information. This risk is minimized by using coded specimens that can only be linked back to personal identifying information through the master key code stored at the DCC. Subjects will not be provided the results of their serum or DNA results since these tests are not expected to be performed in CLIA approved laboratories.

2.8.3.5 Detailed Procedures for Shipping Specimens

Approximately 30 mls of blood should be obtained from all patients who consent (See Appendix 1 for a Sample Consent Form) to the DNA/Blood banking study. A sample will be collected once for each patient, preferably at the baseline visit. For those patients where this is not possible, blood should be collected at the next possible visit.

About half of the drawn blood is sent to Rutgers University Cell Repository for extraction of DNA and plasma, and the other half is sent to Fisher BioServices for serum storage. See Appendix 2 for procedures outlining blood sample collection, shipping and shipping forms for Rutgers University Cell Repository. See Appendix 3 for procedures outlining blood sample collection, shipping and shipping forms for the Biosample Repository at Fisher Bioservices.

Samples for more than one patient can be sent in one shipment as long as there is a separate shipping form for each patient and the tubes are carefully labelled with the correct ID. The ID on the tube label consists of 3 sets of numbers. The first 3 numbers refer to the site number (i.e., Center 1 = site 201, Center 2 = site 202, etc.). The second 5 numbers are the patient study ID, and the last 4 numbers (the Alternate ID) are the military time of the blood draw. Thus, an example of a tube label ID from Center 1 might read: 201 11101 0935.

Note that the shipping forms separate this information into a Sample ID (i.e., site number and study ID) and an Alternate ID (i.e., the military time). Also, the Fisher shipping form requests the 24 hour clock/military time in addition to the Alternate ID. This means filling in the time in two places.

Appendix 1

Sample Consent Form for Blood/DNA Collection

Tissue Storage for Future Use

As part of this study, we are obtaining blood samples from you to prepare and store a sample of your blood serum and DNA. We would like to study your blood serum and DNA in the future, after this study is over. The tests we might want to use to study your blood serum and DAN may not even exist at this time. Therefore, we are asking for your permission to store your blood serum and DNA so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding more about problems that affect people with kidney disease, including vascular access graft failure but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood serum or DNA might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you agree now to future use of your blood and DNA, but decide in the future that you would like to have it removed from future research, you should contact Dr. Bradley S. Dixon, 319-356-1626. However, if some research with your blood serum or DNA has already been completed, the information from that research may still be used. In addition, 2 years after the close of this study (approximately December 2008) the data linking your identity to the samples will be destroyed and there will be no way to identify and retrieve your tissue samples after that date.

This blood and DNA will be sent to the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) Central Repository, a research resource supported by the National Institutes of Health (NIH). The Repository collects, stores, and distributes biological samples and associated data from people with many kinds of disorders. The purpose of this collection is to make samples available for use in research for the study of disorders affecting people with kidney disease, including vascular access graft failure. Your samples will be available to the current study investigators for future use in studying the problem of vascular access graft failure. Your tissue samples will also be available to other qualified investigators studying problems other than vascular access graft failure that affect people with kidney disease.

You may participate in the main study without giving permission for future use of your blood serum or DNA. If you wish to participate in the main study but do not want your blood or DNA stored for use in a future study check the "No" box below. If you agree to allow your blood serum and DNA to be stored at the NIDDK Central Repository, and used by either the current investigators or other investigators studying other problems related to kidney disease, please check the "Yes" box below.

Agree to future use of your blood and DNA stored at the NIDDK Central Repository and available to the current study investigators as well as other future investigators studying disorders that affect people with kidney disease?

Yes ☐ No ☐

Appendix 2

DAC STUDY
FLOW SHEET FOR BLOOD SAMPLE COLLECTION
PURPLE TOP TUBES FOR NIDDK GENETICS INITIATIVE at RUTGERS UNIVERSITY

1) Complete and attach I.D. labels to the tubes. **DO NOT write the patient's name or any other personal identification information (e.g. SS#, DOB) on the tubes.**

2) Collect blood specimen in the 2 purple top tubes with NaEDTA. **Be sure to invert each tube gently 6 times to mix blood with additives and keep them at room temperature.**

3) Double check NIDDK ID #, verify that ID information on tube matches that on the enclosed NIDDK Phlebotomy Collection Form.

4) Date and sign the NIDDK Phlebotomy Collection Form in the TO BE COMPLETED BY PHLEBOTOMIST section.

5) Package the blood tubes in the safety mailer following the enclosed instructions. Be sure to seal the Styrofoam container with the red tape (water resistant).

6) Place the collection form (NIDDK Phlebotomy Collection Form) in the mailer box outside of the plastic bag. Tape cardboard box closed when assembly is complete.

7) Use the enclosed Fed Ex shipping label to ship the sample to the Rutgers University Cell Repository. Be sure shipping label is marked for priority overnight delivery.

8) For routine shipments be sure the outside of the box is labeled "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650."

9) **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**, and a courier will be dispatched to pick up the samples. **Be sure to give Fed Ex the Zip Code of the PICKUP address, not that of the destination.**

10) **Notify Emily Gymnich and Jacqueline Sabb at the Rutgers University Cell and DNA Repository** that blood is being shipped and provide the Federal Express tracking number _____ and NIDDK ID # _____. This can be done by email (gymnich@biology.rutgers.edu; sabb@biology.rutgers.edu;), fax (1-732-445-1149), or phone (1-732-445-1498).

Revised: 1/15/2004

NIDDK GENETICS INITIATIVE

Phlebotomy Form – DAC Study

SHIP AT ROOM TEMPERATURE IN SAFETY MAILER

ENCLOSE A COPY OF THIS FORM WITH BLOOD KIT

FOR RU LAB USE ONLY:

TO: DR. DOUGLAS FUGMAN/GENETICS
RUTGERS UNIV./CELL REPOSITORY
DIV. LIFE SCIENCES – NELSON LABS
604 ALLISON ROAD (RM. C120A)
PISCATAWAY, NJ 08854-8082

FAX: (732) 445-1149
PHONE: (732) 445-1498

EMAIL: **GYMNICH@BIOLOGY.RUTGERS.EDU**
SABB@BIOLOGY.RUTGERS.EDU
SELANDER@BIOLOGY.RUTGERS.EDU

INITIAL: _____

PURPLE ML: _____

ID#: _____

FROM (NIDDK SITE):

Shipment to Include Blood Samples for DNA/Plasma

PURPLE TOP TUBES: ____

NIDDK Staff: PLACE TUBE LABEL HERE OR COMPLETE BY HAND
(VERIFY INFO AGAINST INFO ON BLOOD TUBES!!!)

SEX: M ___ F ___ AGE: _____

SAMPLE ID#: _____

ALTERNATE ID#: _____

TO BE COMPLETED AT COLLECTION SITE (BE SURE TO KEEP A COPY FOR YOUR FILES FOR DATA ENTRY)**:**

IS THE BLOOD HEPARNIZED? (CIRCLE ONE) **YES** **NO**

WHEN WAS THE SAMPLE DRAWN? (CIRCLE ONE) **PRE DRUG** / **ON DRUG** / **POST DRUG**

DATE BLOOD DRAWN: _____ - ____ - ____ (MONTH – DAY – YEAR)

TIME DRAWN: _____ (24 HOURS)

FORM COMPLETED BY: _____

CONTACT THE RUTGERS CELL REPOSITORY TO CONVEY PACKAGE TRACKING NO./DATE OF SHIPMENT (SEE BELOW). IF BLOOD IS SHIPPED ON A FRIDAY FOR SATURDAY DELIVERY, CHECK FEDEX FORM FOR SATURDAY DELIVERY.

EMAILED/FAXED/
CALL IN TO: RUTGERS UNIVERSITY CELL REPOSITORY ____/____/____ _____
(SEE RUTGERS FAX/PHONE #S ABOVE) DATE TIME

PACKAGE TRACKING #: _____ (CHECK SATURDAY DELIVERY ON DELIVERY FORM IF APPLICABLE)

TO BE COMPLETED BY RUTGERS UNIVERSITY CELL REPOSITORY

PRIOR NOTIFICATION REC'D: YES ____ NO ____ - IF YES, DATE/TIME ____/____/____ _____ AM/PM

CONFIRMATION OF RECEIPT OF BLOOD SAMPLE TO NIDDK SITE SENT BY: _____ DATE/TIME ____/____/____

Revision date: 12 Feb 2004

Appendix 3

DAC STUDY
FLOW SHEET FOR BLOOD COLLECTION
Serum Separator (SST) Tubes
for the NIDDK Biosample Repository at Fisher BioServices

1) Complete and attach patient I.D. labels to the tubes. **DO NOT write the patient's name or any other personal information (e.g. SS#, DOB) on the tubes.**

2) Collect the blood in two 7.5 ml SST serum separator (red/gray top) tubes before the draw for the purple top (EDTA) tubes. Be sure to invert each tube gently 5 times to mix the blood with the additives. Keep them at room temperature**.** Let the tubes stand in a rack for at least 30 minutes or until the serum is separated and a clot forms. (Blood containing heparin or warfarin may take longer to clot.) Centrifuge the tubes for 15 minutes at 1300 g (RCF). Move the tubes to the refrigerator until the shipper is ready to go.

3) Complete Section A of the NIDDK Biosample Repository Serum Separator Tube Shipment Form, and include a copy of the form with the shipment. Complete a separate form for each subject.

4) Double check the subject ID, and verify that ID information on tube matches that on the NIDDK Shipment Form. Use the labels provided by the DCC and place them lengthwise on the tubes. Be careful not to cover up the ID when they are wrapped around the tubes.

5) Prepare shipments for FedEx pickup Monday through Thursday. **No Friday shipments, please.** The facility is not scheduled to be opened on Saturday when the package would be delivered. If there must be an exception, please contact us before 3:00pm on Friday. Special arrangements must be made for a Saturday delivery.

6) Assemble the package according to the instructions for the small, refrigerated laboratory shipper (attached).

7) Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339). Give them the account number (in Section 7, Payment, on the pre-printed FedEx Air bill), and your pickup address. FedEx will dispatch a courier to pick up the package.

8) Notify Rich Frome or Heather Higgins at the NIDDK Biosample Repository by email or fax when you schedule the pickup and provide them the Federal Express tracking number(s). Use the following contact information:

Name	**Mobile**
Rich Frome	301.252.6214
Heather Higgins	240.793.0353
Email: BIO-NIDDKRepository@FisherSci.com	
Fax: 301.515.4049	

Revision date: 04 Oct 2005

DAC Study
NIDDK Biosample Repository
Serum Separator Tube Shipment Form

NIDDK Biosample Repository contact information:

Address: Attn: Heather Higgins
Fisher BioServices
NIDDK Biorepository
20301 Century Blvd.
Bldg. 6, Suite 400
Germantown MD 20874

Email: BIO-NIDDKRepository@FisherSci.com

Phone: (301) 252-6214 (Rich)
(240) 793-0353 (Heather)

Fax: (301) 515-4049

Section A: To be completed by the collection site (Send original form to the repository, and retain a copy for your files for data entry.)

Completed by: _____ Date: _____

Name and address of collection site:

Name: _____

Street: _____

City/State/Zip: _____

Sample Information:

Send only samples in 7.5 ml serum separator tubes with red/grey tiger-top caps to repository.

Sample ID#: _____ Alternate ID#: _____

Date blood drawn: ____/____/____ Time drawn: _____ (24 hour clock/ military time)
Month / Day / Year

Is the blood heparinized? (circle one) Yes / No # of SST tubes shipped: _____

When was the sample drawn? (circle one) pre drug / on drug / post drug

Ship samples to the biorepository address listed above. Ship SST tubes on frozen gel packs using the shipping kit provided by the repository. Notify the repository of shipments by email or facsimile on the day the package is picked up by FedEx.

Biorepository notified via (circle one): Fax Email

Biorepository notified by: _____

Date of Notification: ____/____/____ Time: _____AM / PM

FedEx Tracking Number:

Section B: To be completed by the NIDDK Biorepository

Completed by: _____ Date of receipt: ____/____/____

Do the sample Ids on this form correspond with the Ids on the vial labels? Yes / No

If not, describe the error as well as any other discrepancies, and notify a supervisor. _____

_____

_____

_____

Revision date: 04 Oct 2005

Assembling the Small Refrigerated Laboratory Shipper

1. Insert the Vacutainers (SSTs) in the bubble wrap pouch (Saf-T-Pouch).

2. Place the pouch and the white absorbent strip inside the leak proof zip-lock bag. Seal the bag.

3. Place a frozen ice pack in the bottom of the Styrofoam cooler. Put a piece of bubble wrap on top of the ice pack to separate it from the zip-lock bag.

4. Place the bag containing the SSTs on top of the bubble wrap. If necessary, add additional packing to prevent contents from shifting.

5. Put the lid on the cooler and place a copy of the completed NIDDK Serum Separator Tube Shipment Form for each pair of vials on top of the cooler lid. Tubes for two patients may be shipped in the same package.

6. Close and tape the outer cardboard box.

7. Affix the label “UN3373 DIAGNOSTIC SPECIMENS” to the top of the box in the upper left hand corner.

8. Place the repository address label on top of the box in the upper right corner.

9. Use the pre-printed FedEx air bill to ship the specimens to the Fisher BioServices/NIDDK Biorepository. Fill in the date, your name, phone number and return address in Section 1 (leave “Sender’s FedEx account number” blank). In Section 6, check the “No” box, indicating no dangerous goods are in the package. In Section 7, enter “1” under “Total Packages”, and the total weight of the package (2 - 3 lbs). Follow the peel and stick instructions on the back of the air bill to attach it to the side of the box. Tear off the top sheet (sender’s copy) for your records.

10. Please do not send packages on Friday for Saturday delivery; the repository is closed for business on weekends. Samples may be centrifuged and refrigerated until the following Monday. If an exception must be made, please contact the repository no later than 3:00pm on Friday. Special delivery arrangements must be made.

11. **Call Federal Express, 1-800-GO-FEDEX (1-800-463-3339)**. Give them the account number (in Section 7, Payment) and your pickup address. FedEx will dispatch a courier to pick up the package.

04 Oct 2005

3. RANDOMIZATION

3.1 Purpose

Randomization is the point in the study following successful placement of a new arteriovenous graft when the subject is randomly assigned to begin treatment with either Aggrenox or placebo.

3.2 Steps in randomization

All the enrollment data must be completed and the informed consent document signed before a subject can be randomized. The process of randomization consists of completing the steps listed below. The exact details of how randomization is conducted may vary from site to site in order to fulfill each of these steps. The DAC A1 on-line randomization form must be completed for randomization.

1) Identify that the participant has received a new vascular access graft.

a. How to accomplish. A tentative date for surgery is often assigned when the participant sees the vascular access surgeon. However, the exact time of surgery on that date may not be known. Moreover, the date of surgery is also subject to change, often at the last minute due to changes in the schedule of the patient, the surgeon or the operating room. Hence, it is essential that each site develop a method to track changes in the schedule and have the flexibility to accommodate those changes.

   i. Each site should keep an updated calendar listing the tentative date of access surgery for any person that is being evaluated for enrollment into the study.
   ii. The participant should be asked to contact the study coordinator if a change occurs in the schedule
   iii. The study coordinator should check the operating room schedule frequently to look for changes in the schedule
   iv. If possible, provide the surgical scheduler with an updated list of study participants scheduled for a new access and ask them to contact the study coordinator if any change in scheduling occurs.
   v. Talk with the charge nurse in the post-operative recovery room ahead of time about the study. Arrange a mechanism for them to notify the study coordinator that the study participant has completed the access surgery. For instance, on the day of surgery, have a bright colored sheet of paper on the subject's chart that identifies them as participating in the study and asking the post-op recovery room personnel to page the study coordinator when the subject is in the recovery room.

b. Who is responsible? The study investigator working with the study coordinator at each site will be responsible for setting up a system along the lines described above to rapidly identify when a study participant gets an access. The study coordinator at each site will be responsible for carrying out the plan.

2) Confirm that a graft has been placed.

a. How to accomplish. If the surgeon reports that the graft thrombosed in the operating room or in the recovery room, the patient should not be randomized.

3) Notify the DCC and obtain a randomization number.

a. How to accomplish. Randomization is accomplished by logging onto the DAC web site and completing the randomization form. This will result in a screen that provides the subject's randomization number and notifies the DCC that the subject has been entered into the study.

b. Who is responsible? The study coordinator or study investigator at each site is responsible for making sure that subject gets randomized. At some sites, a research pharmacist familiar with the study may dispense the study medication from a research pharmacy. Under this situation it is acceptable for the study coordinator to notify the research pharmacist that the subject is ready to be randomized and designate the research pharmacist to enter the data into the DAC A1 online randomization form to obtain the randomization number. If a research pharmacist will be completing the DAC A1 randomization form then they will need to have a password and be instructed on how to enter data into the DAC database.

c. Where is this exam done? Randomization can be done from any convenient location where there is a computer connected to the internet by a web browser with 128 bit encryption.

When is the randomization done? The optimum time would be immediately after surgery in the second stage post-operative recovery room just before the subject is ready to go home. However, it can be done anytime up to 2 days after surgery that is mutually convenient to the subject and study personnel.

Note: If there was a protocol violation and the wrong type of vascular access was randomized (graft study patient received a fistula), fill out Form 336 - Permanent Discontinuation of Therapy and use code #21. An Annual Check on Vital Status for Inactive Patients Form will be completed based on the enrollment date.

4) Obtain the study drug that matches the bottle numbers.

a. How to accomplish. The bottle numbers obtained for that subject from the DAC website after filling out the online form DAC A1 should be used to match the numbers on two of the bottles of study medication stored at the study site. If no study drug can be found that matches the bottle numbers, the DCC should be contacted immediately on how to proceed. The bottles will also have the confirmation codes, which should be written down before the bottle is dispensed. These codes will be recorded on Form 315 (Pill Dispensing at Randomization Form). The list of drug distribution sites is included as Table 4 in this Manual.

b. Who is responsible? The research pharmacist, study coordinator or study investigator at each site is responsible for making sure that the subject's bottle numbers match two of the samples of study drug stored at the site.

c. Where is the study drug stored? Study medication must be stored in a locked cabinet or room with limited access. This may be the local pharmacy or another secure location at the discretion of the study coordinator and study investigator. Under any circumstance an inventory of study drug must be kept. The inventory must record the date the drug was received, when it was dispensed, who dispensed the drug and who received the study drug along with the recipient's contact information.

d. When is the study drug obtained? The optimum time would be while the subject is in the post-operative recovery room just before the subject is ready to go home. However, it can be done anytime up to 2 days after surgery.

5) Give the participant the first dose of study drug to take and explain how to take it.

a. How to accomplish. A two months supply of study medication will be given to the participant with verbal and written instructions how to take the study medication and any side effects to look for. The study medication is taken as one capsule by mouth twice a day. The study participant will be asked to take their first dose of study medication immediately and a second dose later that same day. A record is placed into the subject's chart and their medication database (if available at that study site) that the subject is on an investigational study drug (Aggrenox or placebo). The subject will be given a wallet-sized card that states that the subject is participating in a trial and is on a study drug containing either Aggrenox or placebo. The card will also have the contact information for the study coordinator and study investigator at the site. The subject will be told to contact the study coordinator if something happens with their study medication or when there are any changes in their medications. A follow-up study visit will be arranged for one month.

Every time you dispense drug, key in the visit form with the masked drug confirmation code immediately.

b. Who is responsible? The research pharmacist, study coordinator or study investigator at each site is responsible for getting the medication to the participant, explaining how to take the medication and making sure that the subject takes the first dose. The study participant will be given a card that lists the name(s) of the study coordinator and study investigator along with their contact information.

c. When is the study drug given? The protocol allows for the initiation of study medication at anytime up to 2 days after surgery. The optimum time would be in the post-operative recovery room after surgery access just before the subject is ready to go home. At this time the subject should be alert enough to understand instructions and take the first dose of medication.

6) Teach the participant to assess for access thrombosis -

a. Rationale. If the participant is not on regular dialysis then it will be important for them to be able to monitor their own access on a regular basis to determine whether it is patent so that the occurrence and timing of the primary endpoint can be accurately assessed.

b. How to accomplish. The access study coordinator should teach all participants how to feel for a thrill in their access and ask that they check the access daily in the morning and notify study personnel or their dialysis physician if they can not feel the thrill in the access. This may be difficult to do in the early post-operative days after access placement if the arm is bandaged and the access thrill is weak but the exam can be done when the bandages are removed for cleaning the suture line. If the assessment of access patency requires auscultation or Doppler examination then the participant will not be able to do this exam. However, in this situation the study coordinator should strongly consider checking on the status of the access in 2 weeks to assess whether it is still patent. This might be coordinated with the post-operative visit to the access surgeon.

c. Who is responsible? The study coordinator at each site is responsible for teaching the participant or their caregiver how to palpate the access for a thrill.

7) Arrange follow-up.

a. How to accomplish. Set a time to meet with the participant for their first monthly study visit after access placement. If they are already on regular hemodialysis then this should be at one of their dialysis treatments. If they are not yet on hemodialysis then a mutually acceptable time and place should be set for the first monthly visit. It is possible that the participant may start on dialysis before one month is up. If so, the participant should be asked to contact the study coordinator to let them know that they have started on dialysis and arrange a new time and place to meet. As a fail-safe, the study coordinator should contact the dialysis unit where the participant will be starting dialysis and ask them to notify the study coordinator when the participant is scheduled to start dialysis.

b. Who is responsible? The study coordinator at each site is responsible for arranging follow-up and tracking when the subject starts on regular hemodialysis.

4. STUDY TREATMENT PLAN

4.1 Study visits

4.1.1 Purpose

The purpose of the study visits is to: 1) assess access function and monitor for the development of access stenosis using flow monitoring (see MOP, section 5), 2) obtain information on all access-related events and procedures relevant to the primary and secondary outcomes (see MOP, section 6), 3) determine whether there have been changes in the medical condition or medications that might influence access survival or require discontinuation of the study medication (see MOP, section 6), 4) report any adverse complications of the study medication (see MOP, section 6), 5) assess and encourage compliance with the study medication and follow-up, 6) collect old study containers and provide a new 1 month supply of study medication (see MOP, section 4.2).

4.1.2 Frequency of the study visits

The study visits are to be done every 4 weeks starting from the date of randomization. If a visit is missed, then a new visit must be scheduled as soon as possible. The date of the next monthly visit (after the missed visit) should continue to be on the original schedule based on the randomization date and not delayed as a result of the missed appointment. (For example, if the visit was scheduled for May 1st but was missed and rescheduled for May 6th, the next visit in 4 weeks should be on May 29th and not June 3rd).

4.1.3 Duration of study visits

Subjects will be followed monthly until: 1) the first monthly visit after the primary endpoint, 2) the patient withdraws from the study or 3) the end of the study.

4.1.4 Who does the study visits

The monthly visits will be performed by the study coordinator or study investigator at the site. A separate person who has been trained in performing flow monitoring may do the monthly flow monitoring at a time different from the monthly study visits (see MOP, flow monitoring, section 5).

4.1.5 Location of the study visits

The monthly study visits should involve face-to face contact between the study personnel and the participant. The location can be arranged to best suit the needs of the participant and the study personnel. If possible, the participant's recent medical and dialysis records should be available for review at the meeting. For participants who are on hemodialysis the optimum site for these visits is probably in the hemodialysis unit at the time of one of the participant's regularly scheduled dialysis sessions. For participants not yet on hemodialysis then the monthly visit might occur in the study investigator's clinic or dialysis unit as appropriate.

4.2 Study drug administration

4.2.1 Study drug

Aggrenox and matching placebo will be provided by Boehringer-Ingelheim. Participants will receive either the study medication Aggrenox or an identical capsule that contains placebo. Aggrenox is a combination of 200 mg of sustained-release dipyridamole along with 25 mg of enteric coated aspirin. Dipyridamole has several actions, one of which is to block adenosine uptake and thereby promote vasodilatation and inhibit vascular smooth muscle cell proliferation. Aspirin inhibits platelet aggregation by irreversibly acetylating cyclooxygenase and thereby blocking formation of prostaglandins involved in platelet aggregation. The participants will be asked to take 1 capsule of the assigned study drug by mouth twice a day.

Double blind study - The study is double-blinded so that neither the participant nor the study personnel know whether the participant is on Aggrenox or the placebo. The blinded trial design is important because bias might be introduced if the participants or the study personnel know what treatment they are receiving.

Dispensing study medication – A new bottle of study medication will be dispensed every 4 weeks. In order to view the bottle that is currently reserved, go to the DAC main menu and click on Reports. Click on Graft randomized bottle report and fill in the ID and name code. Press "Get Bottle Report". The previous form 316 must be completed in order to get the new bottle. The participant will be asked to return the old empty bottle of study medication at that time. Additional bottles may be dispensed if the participant plans to be out of town at the time of the next 4 week visit.

Who dispenses medication to participant – It is preferable for the study coordinator to dispense the new study medication at each 4 week study visit. However, the study medication can also be dispensed from the local pharmacy if appropriate arrangements have been made.

Duration of study drug administration – The participant will remain on the study drug until one of the following events occur:
They reach the primary composite endpoint of either access thrombosis or an access procedure done to maintain or restore access function.
An adverse event occurs that requires stopping the study medication (see below)
The study is terminated (see below)

Management of Adverse Events, Change in Medications and Interruptions in Treatment -

Who to contact - At the time of enrollment, participants will be provided with an information card containing a description of the study and 24 hour contact information for the study personnel. They should be asked to keep this card with them at all times while they are in the study. The purpose of

the information card is to facilitate rapid communication with study personnel if an adverse event occurs or there is a change in concomitant medications or an interruption in study treatment needs to be considered.

1. Non-emergent concerns - The participant should be advised to contact the study coordinator or study investigator if they have any non-emergent concerns about possible adverse effects of the study medication or are concerned about whether a new medication might interact with the study medication.
2. Emergencies - If an emergency situation arises, such as severe bleeding or chest pain, the study participant should seek immediate attention by their primary physician or the local emergency room. The emergency room or primary care physician can then contact study personnel regarding any questions about the study medication.

Reducing the Dosage - In case the participants experience intolerable level side effects, which are consistent with those reported for Aggrenox, the medication should be withheld and later re-challenged. Common reasons that might lead to prescription of a reduced dose include headache, dizziness, abdominal pain, heartburn/dyspepsia, nausea/vomiting, diarrhea and hypotension. The study drug could be restarted at a lower dose and then titrated up to 2 capsules per day as tolerated. Study Form 317 should be filled out to document the reduced dose.

Unmasking - Aggrenox has a small dose of aspirin that could predispose to bleeding. We anticipate that unmasking may be required in the following two circumstances: 1) prior to the performance of emergency surgery and 2) if there is life-threatening hemorrhage where the transfusion of platelets to reverse the antiplatelet effects of therapy is indicated. When the physicians at the clinical center agree it is absolutely necessary that a study medication code be released, the Data Coordinating Center will reveal the medication for a given patient to the study nephrologist at the facility. A list of approved physicians provided by the Clinical Centers is on file at the DCC. The list also includes current P.I's and Co-P.I.'s. A physician must be on the list to request emergency unmasking. After unmasking, the patient should be continued in the trial on study medication if the subject did not have a major or life-threatening bleed and there are no other medical contraindications to doing so.

4.2.2.1 How to release the study treatment assignment

1. For an emergency unmasking between the hours of 8:00 a.m. and 5:00 p.m. (Eastern Time) the Data Coordinating Center will unmasking the treatment assignment after obtaining agreement from a Clinical Center Principal Investigator different from the patient's center. Contact the DCC [(216-444-4366 (secretary), 216-444-9927 (Dr. Beck), 216-444-9938 (Dr. Gassman), 216-445-7849 (Ms. Weiss), or 216-445-9450 (Mrs. Radeva)] and provide a detailed clinical explanation for unmasking. Explain what will be done differently on the basis of which masked medication the person was on. Also, provide the following information:

   My name is Dr. X
   I am from DAC Clinical Center at _____
   I want to be unmasked for patient (ID#, Name Code)

2. For an emergency unmasking between the hours of 5:00 p.m. and 8:00 a.m. (Eastern Time), the Clinical Center's Principal Investigator may telephone the Cleveland Clinic Hospital Pharmacy at 216-444-5191 and say:

   My name is Dr. X

I am from DAC Clinical Center _____
I want to be unmasked for patient (ID#, Name Code)
The Dialysis Access Consortium (DAC) Study Book is located in the I.V. Room

The physician will then be given the patient's treatment assignment.

If at all possible, the patient should be kept masked.

An unmasking Form 384 must be entered if unmasking the patient's randomized medication occurs. If after unmasking the Principal Investigator decides that a stop point is not needed, a Form 384 must still be entered with a description explaining the factors that led up to the need for the unmasking.
Unmasked patients should continue to be followed according to the usual data collection schedule.

4.3 Bleeding

4.3.1 Classification of bleeding

Aggrenox has a small dose of aspirin that will increase the risk of bleeding. Bleeding will be classified as minor, intermediate, major, life-threatening or fatal. A description of each category is included in the protocol.
An intraocular bleed is defined as a vitreous hemorrhage or a bleed in the eye that leads to sustained loss of vision. When an intraocular bleed meets this definition, it is classified as a major bleed and study drug must be permanently discontinued. In other cases of retinal vessel bleeds, the patient's ophthalmologist should be consulted as to whether study drug may be continued.

4.3.2 Surgery or other invasive procedures

4.3.2.1 Elective surgery

If the patient requires elective surgery or other invasive procedures with a risk of bleeding, the study medication should be stopped 7 days prior to the procedure and resumed the day after the procedure if there has not been inordinate bleeding and if the physician performing the procedure agrees. This temporary cessation of medication does NOT require that the medication code be revealed (i.e. unmasking). DAC study form 335 must be filled out.

4.3.2.2 Emergent surgery with high adverse risk of bleeding

If the patient requires emergent surgery where the risk for bleeding is high (e.g., neurosurgery) the study medication should be stopped and consideration given to revealing the medication code (unmasking) and administering platelet transfusion if the patient has been receiving active drug. DAC study form 335 (temporary discontinuation) or form 336 (permanent discontinuation) must be completed.

4.3.3 Other adverse events

4.3.3.1 Headaches and diarrhea

Aggrenox has been associated with a higher incidence of headaches and GI disturbances, particularly diarrhea compared to placebo. However, these tend to get better with continued use of the drug. If these events occur, efforts should be made to treat them conservatively (e.g., acetaminophen for headache or psyllium for diarrhea) and continue the study medication. If the symptoms persist then a trial of withdrawing the study medication for a week can be performed to see if the symptoms resolve. If the symptoms do resolve and the subject agrees, rechallenge with the study medication

should be considered to confirm that it is the cause of the symptoms before stopping the study medication completely. A committee of study investigators will review the reasons leading to permanent withdrawal from therapy.

4.3.4 Concomitant medications

4.3.4.1 Contraindicated medications

Anticoagulants, antiplatelet agents and non-steroidal anti-inflammatory drugs. Since Aggrenox contains a low dose of aspirin, participants may be on aspirin and still participate in the study. In addition, the use of intermittant heparin for dialysis is not contraindicated. Every effort should be made to avoid the use of anticoagulants (e.g., warfarin), antiplatelet agents (e.g., clopidogrel, ticlopidine or sulfinpyrazone) or nonsteroidal anti-inflammatory agents (e.g., ibuprofen) in patients while on study medication. The study coordinator will track medications during each monthly study visit (see MOP, section 6). A list of commonly prescribed types of these medications is shown in Table 1. This list is not complete and new medications will come on the market during the study, so be sure to check any medication to determine whether it can be classified as one of these three classes of medicines. If there is uncertainty about a medication, then contact the principal investigator or the local pharmacist for clarification.

4.3.4.2 Rationale

The risk of bleeding is likely to be increased if Aggrenox is used in combination with anticoagulants or antiplatelet agents. In addition, the risk of GI complications including ulcers is likely to be increased by combined use of Aggrenox with nonsteroidal anti-inflammatory agents.

Initiation of therapy with a contraindicated medication – If there is an absolute medical indication for any of these contraindicated agents (e.g., anticoagulants for atrial fibrillation or deep venous thrombosis) then therapy with the study medication must be discontinued. The medication assignment will remain masked and patient will continue to be followed for the duration of the study as per the study plan. Likewise, if a medical requirement for Aggrenox or dipyridamole arises then the study medication will be stopped and the patient followed for the duration of the study. The use of aspirin for an accepted medical indication (e.g., unstable angina or secondary prevention of stroke or myocardial infarction) or the use of intermittent heparin for hemodialysis will not constitute a reason for stopping the study medication.

Management of pain or fever - Management of pain should be attempted first with acetaminophen, codeine or other analgesics. A fever should be managed with acetaminophen. However, use of aspirin is not contraindicated for either pain control or fever if absolutely necessary.

Discontinuation of Therapy - Adverse events leading to cessation of study drug but not termination from the study are listed below. Remember to fill out DAC study form 336. You should continue to fill out the monthly forms.

Development of an intestinal ulcer or gastrointestinal bleeding while on the study medication.
An adverse event attributed to the study medication such as intolerable persistent headache, diarrhea or dizziness without other etiology that does not respond to medical management.
A bleeding disorder (e.g., a major or life-threatening bleed) that contraindicates the continued use of Aggrenox.
A new medical requirement for long-term anticoagulation or antiplatelet therapy other than aspirin.
A new medical requirement for using Aggrenox or dipyridamole.

Events Leading to Withdrawal from the Study - A patient will be withdrawn from the study for the reasons listed below. Fill out DAC study form 336.

1. The participant dies.
2. The participant is lost to follow-up, due to permanent transfer to another renal replacement modality or to a non-participating dialysis unit.
3. Participant withdraws their consent.

4.4 Study completion

Study participation will end at one of the 3 events listed below occurs. Study medication will be withdrawn at the time of study completion.

1. The first monthly visit following the primary endpoint.
2. Patient withdrawal due to one of the reasons listed in Section 4.4.
3. The study ends.

Enrollment In Competing Studies

A patient may be enrolled in a competing study 30 days after study drug is discontinued or 30 days after the primary endpoint (whichever comes later).

Appendix: Unmasking Physicians List

UNMASKING TREATMENT ASSIGNMENT
PHYSICIAN LIST

Laura Dember, M.D. (Fistula Study)	phone: 617-638-7331 pager: 617-638-5795 beeper #4213
Brad Dixon, M.D. (Graft Study)	phone: 319-356-1626

Alternates:

James Kaufman, M.D.	phone: 857-364-5613
Lawrence Hunsicker, M.D.	phone: 319-356-4763
Cathy Meyers, M.D.	phone: 301-451-4901

Approved Physician List from the Clinical Centers

Center 1

Laura Dember, M.D.
James Kaufman, M.D.
Marguerite Hawley, M.D.

Baystate

Dr. Gregory Braden (PI)
Dr. Michael O'Shea
Dr. Jiuming Ye
Dr. Jeffrey Mulhern
Dr. Steven Sweet
Dr. Barbara Greco
Dr. Anthony Poindexter
Dr. David Poppel
Dr. Michael Germain

Center 2

Arthur Greenberg, M.D.
Mike Berkoben, M.D.

Center 3

University of Iowa

Brad Dixon, M.D.
Lawrence Hunsicker, M.D.

Peoria

Robert Pflederer, M.D.
Kent Bryan, M.D.
Frederick Horvath, M.D.
Phillip Olsson, M.D.
Robert Sparrow, M.D.

Ben Pflederer, M.D.
David Rosborough, M.D.
Tim Pflederer, M.D.
Paul Dreyer, M.D.
Gordon James, M.D.
Frank Darras, M.D.
Beverly Ketel, M.D.

Center 4

Jonathan Himmelfarb, M.D.
James Whiting M.D.

Center 5

Miguel Vazquez, M.D.
Ramesh Saxena, M.D., Ph.D.
Shujun Li, M.D.
R. James Valentine, M.D.
Andrew Fenves, M.D.
Ingemar Davidson, M.D.
Devasmita Dev, M.D.
Henry Quinones, M.D.
Elizabeth Kuo, M.D.
Jeff Penfield, M.D.
Biff Palmer, M.D.
Anitha Toke, M.D.

Center 6

Mike Allon, M.D.
Michelle Robbin, M.D.

Center 7

Jay Delmez, M.D.
Brent Miller, M.D.
Marcus Rothstein, M.D.
David Windus, M.D.
Daniel Coyne, M.D.
Anitha Vijayan, M.D.
Graeme Mindel, M.D.
Irmantas Juknevicius, M.D.
Matthew Koch, M.D.
Will Ross, M.D.

Center 8

Tom Golper, M.D.
Gerald Schulman, M.D.
Julia Lewis, M.D.
Neelam Bhalla, M.D.
Anthony Langone, M.D.

Center 10

Dr. Asif Rahman (PI)
Dr. Julian Espiritu
Dr. Shabih
Dr. R.V. Lamb

Center 11

Dr. Jack Work

Center 12

Kevin J. Martin, MB, BCh, FACP
Mary E. Gellens, M.D.

Center 13

James R. Cotton, M.D.
Nabeel Ahmed, M.D.
Stefanie Diaz, M.D.
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Center 14

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5. FLOW MONITORING

5.1 Rationale

Flow monitoring is used to detect a decrease in access flow rate that is predictive of the development of access stenosis and an increased risk of thrombosis. Guidelines from the Dialysis Outcomes Quality Initiative (DOQI) recommend an organized approach to access surveillance with regular assessment and tracking of access function to detect and treat access stenosis. Flow monitoring is the best mechanism to make this assessment. In addition, flow monitoring provides an important tool to monitor the development of access stenosis and better assess the mechanism of action of the study drug.

5.2 Who does the flow monitoring?

The study coordinator or a dialysis technician will do the measurement of access flow rate. Study personnel who do the flow monitoring must have received training and demonstrated competence in making the measurements. To limit variability, only one or two trained personnel at each site should do the flow measurements.

5.3 Where is the flow monitoring done?

Monitoring will be done during one of the participant's regularly scheduled hemodialysis sessions. Participant's who are not on hemodialysis or are not using their new graft for dialysis will not have their blood flow measured until they start dialysis.

5.4 Time table for flow monitoring

5.4.1 The first flow measurement

The first flow will be obtained as soon as possible after starting to use the access but no more than two weeks after starting to use the access for dialysis. The goal is to get the earliest possible flow measurement as soon as possible after access creation. The goal is to get the first access flow measurement in most participants within the first week after access creation.

5.4.2 The second flow measurement

The second flow measurement will be obtained approximately two weeks after the first flow measurement. This second measurement should be no sooner than 1 week and not more than 1 month after the first measurement of vascular access flow. The goal is to get a second measurement close to the first so as to have a good baseline flow measurement for future comparisons of access flow.
Flow measurements every 4 weeks – After the first two flow measurements, access flow measurements will be obtained at 4 week intervals timed from the date of the first access flow measurement. Flow measurements will be done every 4 weeks up to and including one month after the primary endpoint occurs (thrombosis or an access procedure to restore or maintain access function) or until study termination.

5.4.3 Repeat a critical flow measurement

When a flow measurement is found to meet criteria for access evaluation (see below) it is recommended that the results be validated with repeat flow measurement at a different dialysis session before sending the patient for angiography. This second confirmatory measurement should be done as soon as possible preferably within 2 weeks after the first measurement that met criteria for access evaluation. The data is recorded on DAC study form 353. If the study team does any other flow measurements on the participant during the time they are in the trial then these measurements should also be reported on form 353.

5.4.4 One flow measurement after the primary endpoint

The flow measurement after the primary endpoint should be obtained as soon as possible after a corrective procedure is done to restore or maintain access flow. The goal of this measurement is to confirm that the angioplasty improved access flow and to determine the degree of correction in flow. If the access fails completely and no flow is restored in that access then no flow measurement after the primary endpoint is required.

5.4.5 Missed flow measurements

If a scheduled flow measurement is missed then it should be done at the next hemodialysis session or as soon as possible after the missed measurement. All subsequent flow-monitoring should remain on the original 4 week schedule based on the date of the first flow measurement and not be "reset" by the missed measurement.

5.4.6 Documentation of flow measurements

DAC study form 353 must be completed for each day that access flow measurements are done.

5.5 Training for flow monitoring

5.5.1 Who will be trained?

Any personnel who does flow monitoring on study participants must be trained prior to doing the flow measurements and entering data into the database. At least one person and preferably two people at each study site must be trained in the technique at all times.

5.5.2 Who is responsible for doing the training?

A representative of Transonic will do the initial training on the proper use of their HD02 access flow monitoring units. Another member of the study team who has received training and is qualified in flow monitoring must train any new personnel who missed the initial training. It will be the responsibility of the investigator at each site to make sure that the study personnel at their site have received training and are qualified to do the flow monitoring.

5.5.3 Location and timing of the first training session

The initial training session will be done as needed at a designated hemodialysis unit at each of the 7 primary study centers. As many of the personnel that require training should be present at that site for this initial training session. This training will be done prior to the start of the full-scale trial. Trained study personnel on site will do the training of new personnel at a time and place that is mutually acceptable and considered appropriate by the principal investigator.

5.6 Quality Control for the Study Endpoint

5.6.1 Fistulogram evaluation

Rationale

The primary outcome measures for the Graft Study are either: 1) thrombosis, or 2) an access procedure performed or recommended to restore patency including angioplasty, thrombolysis, thrombectomy, or any surgical modification of the graft. The stipulated degree of access stenosis that would prompt a recommendation for a procedure is a stenosis $\geq$ 50%. The Quality Control and Improvement Committee requires a method of determining consistency and accuracy of the fistulogram readings across all interventional laboratories involved in the Dialysis Access Consortium studies. To facilitate this, a Central Radiology Reading Center (CRRC) will review four fistulograms from each interventional laboratory. The Vascular and Interventional Radiology Department at Duke University Medical Center has been designated as the CRRC. The

fistulograms/angiograms will be over-read by a blinded observer for degree of agreement with the clinical department, compliance with the requirement to use orthogonal views, and technical adequacy of the films. Fistulograms/angiograms will be classified as no stenosis, <50%, between 50 and 95%, near total (>95%), or can't tell.

Procedure for coding and forwarding fistulograms and report

Centers will remove all protected health information (PHI) from both the films and the dictated reports before sending them to Duke. Label each with an identification code generated as described below. Seal the printed report in an envelope labeled with the same identification code. The identification code will consist of the DAC Center number, a letter signifying the radiology department, a hyphen, the film number, a hyphen and the PID. For example, a Duke label for a film from the first radiology department would be 2A-01-020050 for the first film and 2A-02-020051 for the second film. Each DAC center will create its own radiology department identification letters and use them consistently for films sent from that radiology department. The list of these centers should be sent to the CRRC separately. For example if center 3 (Iowa) has ten radiology departments the first film label for the eighth listed radiology center could read 3H-01-030021.

The first four fistulograms/angiograms AND related dictated reports from each individual interventional center should be sent to Duke University Medical Center to the attention of Joanna Hiller:

Joanna Y. Hiller, RN, MSN, ANP-C
Nurse Practitioner
Vascular/Interventional Radiology
Erwin Road
Duke Hospital North, Room 1502
Durham, NC 27710
Phone: 919-684-7280
Fax: 919-684-7148
Email address: hille006@mc.duke.edu

The method of delivery is left to the discretion of each sending center. Films will not be returned. Once the films are received at Duke University Medical Center they will be reviewed and a corresponding form will be completed. The criteria entered for each form will include information based on the number of views, technical adequacy, stenosis grade, whether an intervention was done and general assessment and comments. This data will be entered into the computer and the DCC will send reports back to the local centers. In the absence of a discrepancy, further review for that laboratory will not be performed. In the event of a significant discrepancy, the center will be referred to the Quality Control Committee for development of ongoing monitoring for that laboratory and discussions with the center PI.

5.6.2 Access flow measurement

1. Transonics Flow Measurement Systems will be tested before each patient measurement. The blood pump from the dialysis machine will be set at 200 mL/minute flow with pre-pump pressure of <100 mmHg. If more than a 5% flow measurement discrepancy occurs between the Transonic system and the hemodialysis machine, the HD machine blood pump will be recalibrated. If the discrepancy persists the Transonic system will be recalibrated by the manufacturer. Yearly recalibration of individual Transonic systems will be performed by the manufacturer.

2. Access flows will be determined on successive treatment days on randomly-selected patients at each center to determine reproducibility of measurements. This will be done on patients randomly assigned by the DCC. One patient at each center will be randomly assigned per month. The DCC will ensure that individual units within the center are tested with equal frequency. Variability >25% will be reported to the CQI committee.

Access flow will be measured within 2 weeks of an angioplasty to determine success of the procedure.

5.7 Procedures for measurement of access flow

5.7.1 Data to collect at each visit

Enter data on DAC study form 353.

1. Blood pressure – measured at the time of the access flow.
2. Time access flow measurement done – Recorded using 24-hour clock.
3. Time dialysis started - Recorded using 24-hour clock. NOTE: the access flow measurement should be obtained as soon as possible after starting dialysis and must be made within the first 2 hours after starting dialysis.
4. Dialysis pump blood flow reading – Blood flow reading obtained from the dialysis machine.
5. Mechanism for infusing saline – "Release" refers to allowing saline to enter the dialysis tubing from a bag of saline hanging at the dialysis machine and connected to the tubing. "Injection" refers to injecting a known bolus of saline into the dialysis tubing using a syringe.
6. Measured blood flow reading – Measured dialysis blood flow from the Transonic monitor.
7. Measured recirculation – Two measurements done with lines in normal orientation for dialysis.
8. Measured access flow – Reverse dialysis lines for this measurement. Make two measurements of access flow. If they differ by more than 10%, a third measurement is required If the third measurement differs by more than 107 from the average access blood flow of the first two, a fourth measurement should be obtained. Record all measurements.
9. Normalized blood flow (nQb) – This will be calculated by the DCC using the equation listed in section 5.7.2 above.
10. Mean normalized blood flow – This will be calculated by the DCC for each visit by taking the average of all the normalized blood flow measurements done at that visit.

5.7.2 Protocol for measurement of recirculation and access flow

Streamlined description of the access flow monitoring technique using the Transonic Systems, Inc. flow/dilution sensor.

Introduction

The following text summarizes approximately 15 pages of the operator's manual that describe instrument setup and access blood flow measurement using the Transonic Systems, Inc. HD02 flow monitor. HD01 flow monitors can also be used but are not described here. Procedures for instrument testing and calibration are not included here but can be found in the manual. The Transonic Systems technique differs from previous methods for measuring access flow in several respects. The "new" method is an indirect measurement that relies on the Fick principle of indicator dilution. As such it can be performed only during hemodialysis treatments while blood is flowing from the access device to the dialyzer and back to the access device. No manipulation of or access to the patient's arm is required for the measurement. This method also benefits from the mixing effect of turbulent flow

through the access device that interferes with flow measurements by Doppler frequency shift techniques.

The procedure begins with measurement of access recirculation because it is relatively simple to do, adds only 2-3 minutes to the total measurement time of approximately 20 minutes, and helps to identify and locate stenoses in the mid-portion of the graft (between the needles). Measurement of recirculation is essentially identical to measurement of access flow except that the dialysis lines are not reversed. As practiced in the dialysis clinics at the University of California, Davis where much of the technology for access flow measurements by indicator dilution was developed, this procedure does not differ from that described in the manual.

The matched flow/dilution sensors provided by Transonic Systems, Inc. are individually calibrated for the dialyzer tubing used in the clinic. Sensors from different instruments are not interchangeable. The instrument must be recalibrated when a sensor is mounted on a different type of dialyzer tubing. At U.C. Davis this has not been a problem since all patients are dialyzed with the same brand of tubing.

Ultrasound velocity varies slightly with blood temperature, so it is assumed that all flow and recirculation measurements are performed with the blood at 37^{o}C.

The velocity of ultrasound is higher in blood compared to normal saline (which is the principle that allows detection of the saline bolus) so calibration of the instrument with normal saline is not possible.

The following procedures describe the saline "release" method for injecting the indicator. The alternative saline "injection" method may be required in some patients. The latter requires a syringe for injection of a saline bolus but is otherwise identical to the saline release method.

Equipment list

- Transonic Systems Inc. HD02 System
  - Flow monitor
  - 2 flow/dilution sensors with cables to the monitor
  - Computer: PC running Windows 95,98, or NT
  - Serial cable from PC to the monitor
  - Software: ***Access Flow and Recirculation*** developed by Transonic Systems, Inc.
- Normal saline for injection (1000 ml bag) at room temperature
- Line (with clamp) from saline bag to the pre-pump port in the dialysis circuit
- Vaseline
- Flow sheet

Setup

- Identify patients for access flow measurements before starting their dialysis treatments.
- Place the arterial (dialyzer inflow) needle into the fistula or graft in the opposite direction to flow in the access device and place the venous return needle in the same direction as flow.
- Begin the following procedure for measuring access recirculation and flow approximately 30 to 60 min after starting dialysis.
- Select a site on the arterial and on the venous dialyzer tubing 5-10 cm (2-4 inches) from the dialysis needle connections.

- Apply a layer of Vaseline to the tubing surface to enable transmission of ultrasound.
- Mount the flow/dilution sensors by clamping them to the tubing at the lubricated sites.
- Plug the two cables from the flow/dilution sensors into the appropriate ports on the monitor.
- Connect the computer and monitor using the 9-pin serial cable and serial port. Either Com 1 or Com 2 may be used but Com 2 will require a RS232 cable adapter.
- Plug the monitor into a hospital grade electrical outlet.
- Turn on the monitor power switch.
- Turn on the computer.
- Once blood or saline is flowing in the tubing, check the “% ultrasound” message on the monitor LCD. If less than 60%, remove the sensors, re-apply Vaseline, and re-mount.
- Calibration (optional)
  - ✓ Enter Program Mode by simultaneously depressing both arrow buttons on the flow monitor.
  - ✓ Turn off ultrafiltration
  - ✓ Turn the blood pump off and adjust the zero offset for each sensor (this must be repeated whenever a sensor is moved to another site).
  - ✓ Select the tubing for which the sensor was calibrated.
  - ✓ If necessary, adjust the venous sensor flow calibration (normally not required).
  - ✓ Exit Program Mode.

Procedure for measuring access recirculation during dialysis

- Adjust the blood pump rate to the usual dialysis setting (close to maximum) and turn ultrafiltration on (if previously shut off).
- Record the patient's arterial blood pressure and time on the flow sheet.
- Load the Transonic Systems, Inc. software by clicking on the icon "Access Flow and Recirc."
- Select "New Patient" on the Main Menu bar, then either "Select Patient" or "Add Patient" as appropriate from the pull-down menus.
- Enter the requested data (BP, type of access, blood pump and monitor flow readings) and exit.
- Select "Recirculation" on the main menu bar and choose "Record to disk."
- Follow the instructions given on the screen to spread the venous and arterial pressure alarm limits.
- When instructed, release the clamp on the saline bag for a 4 to 5 second count (~20 ml). Do not clamp off the arterial line flow proximally as is done during line flushing. If an error occurs, the computer will prompt for another infusion.
- If the computer screen indicates "no recirculation" stop the computer acquisition and proceed to measure access flow.
- If a percentage recirculation is shown (> 5%), stop the computer acquisition, record the percentage on the flow sheet, and repeat the infusion.
-

Procedure for measuring access flow

- Stop the blood pump and using universal precautions (gown, gloves, shield/mask) reverse the lines at the needle hubs.
- Set the dialyzer blood pump to 300 ml/min and set the prescribed ultrafiltration rate.
- Record the patient's arterial blood pressure and time on the flow sheet.
- Select "Access Flow" on the main menu bar and choose "Record to disk."

- When instructed, release the clamp on the saline bag for a 4 to 5 second count (20-25 ml). Do not clamp off the arterial line flow proximally as is done during line flushing. If an error occurs, the computer will prompt for another infusion.
- Stop the computer acquisition, record the access flow rate, and repeat the infusion.
- If the difference between the two flows is greater than 10% of the flow, do a third infusion.
- Stop the blood pump and return the lines to their normal (non-reversed) configuration using universal precautions.
- Restore the patient's prescribed blood flow and ultrafiltration rates.
- Record the recirculation percentages (if any) and blood flow rates in the patient's chart.

Flow sheet

Patient name:

ID number:

Date:

Access description:

RECIRCULATION				
File name				
Measurement number	1	2	3	4
Dilution type (circle)	release / inject	release / inject	release / inject	release / inject
Time (24 hr clock)				
Patient BP (mm Hg)				
Monitor Qb (ml/min)				
Blood Pump Qb (ml/min)				
Recirculation (%)				

ACCESS BLOOD FLOW				
File name				
Measurement number	1	2	3	4
Dilution type (circle)	release / inject	release / inject	release / inject	release / inject
Time (24 hr clock)				
Patient BP (mm Hg)				
Monitor Qb (ml/min)				
Blood Pump Qb (ml/min)				
Access flow (ml/min)				

Diagram of access fistula or graft:

Equipment list

- Transonic Systems Inc. HD02 System

Flow monitor

2 flow/dilution sensors with cables to the monitor

Computer: PC running Windows 95, 98, or NT

Serial cable from PC to the monitor

Software: ***Access Flow and Recirculation*** developed by Transonic Systems, Inc.

- Normal saline for injection (1000 ml bag) at room temperature
- Line (with clamp) from saline bag to the pre-pump port in the dialysis circuit
- Vaseline
- Flow sheet

Figure 5.1
Flow Diagram for AVG Surveillance - Calculating First Baseline

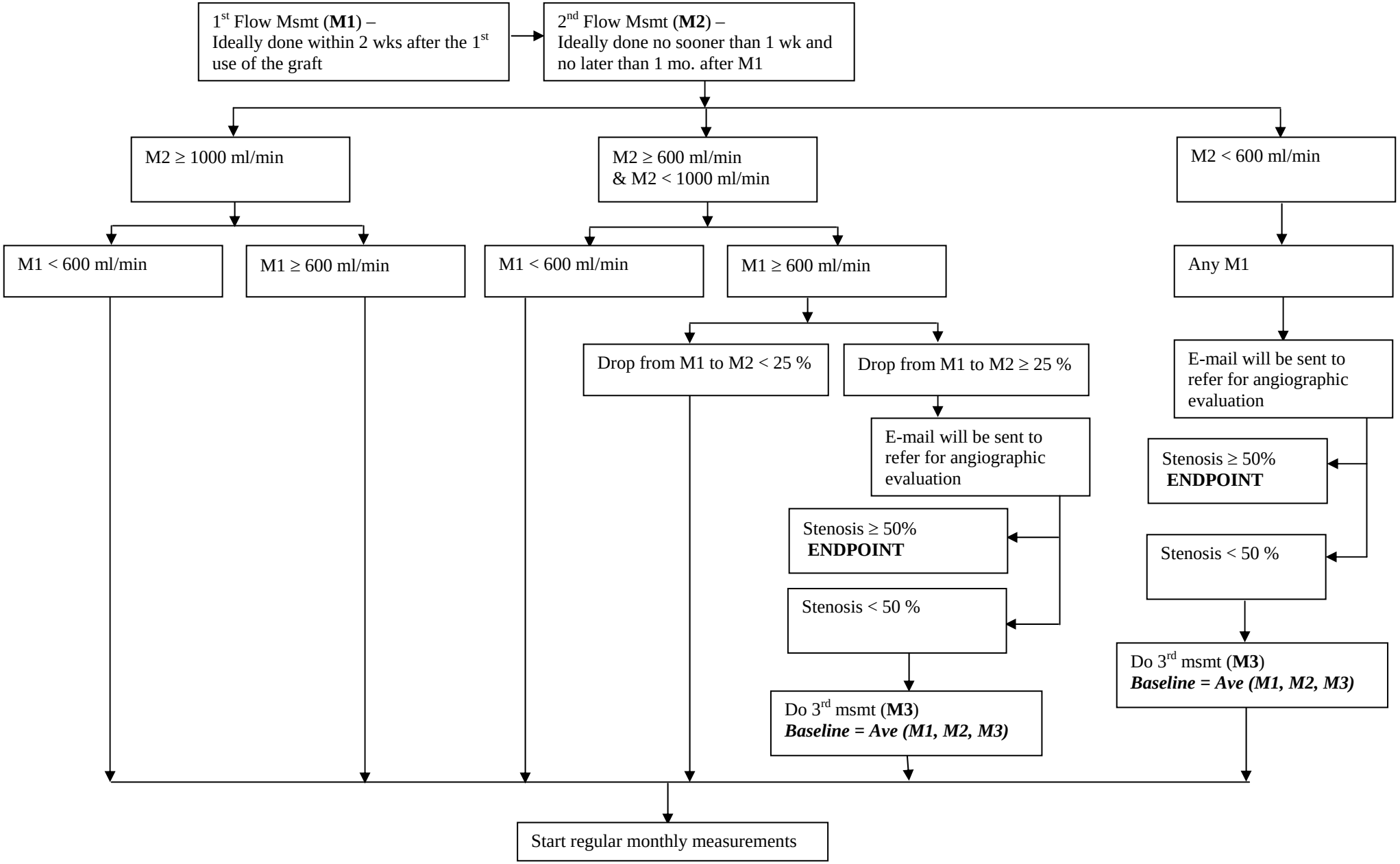
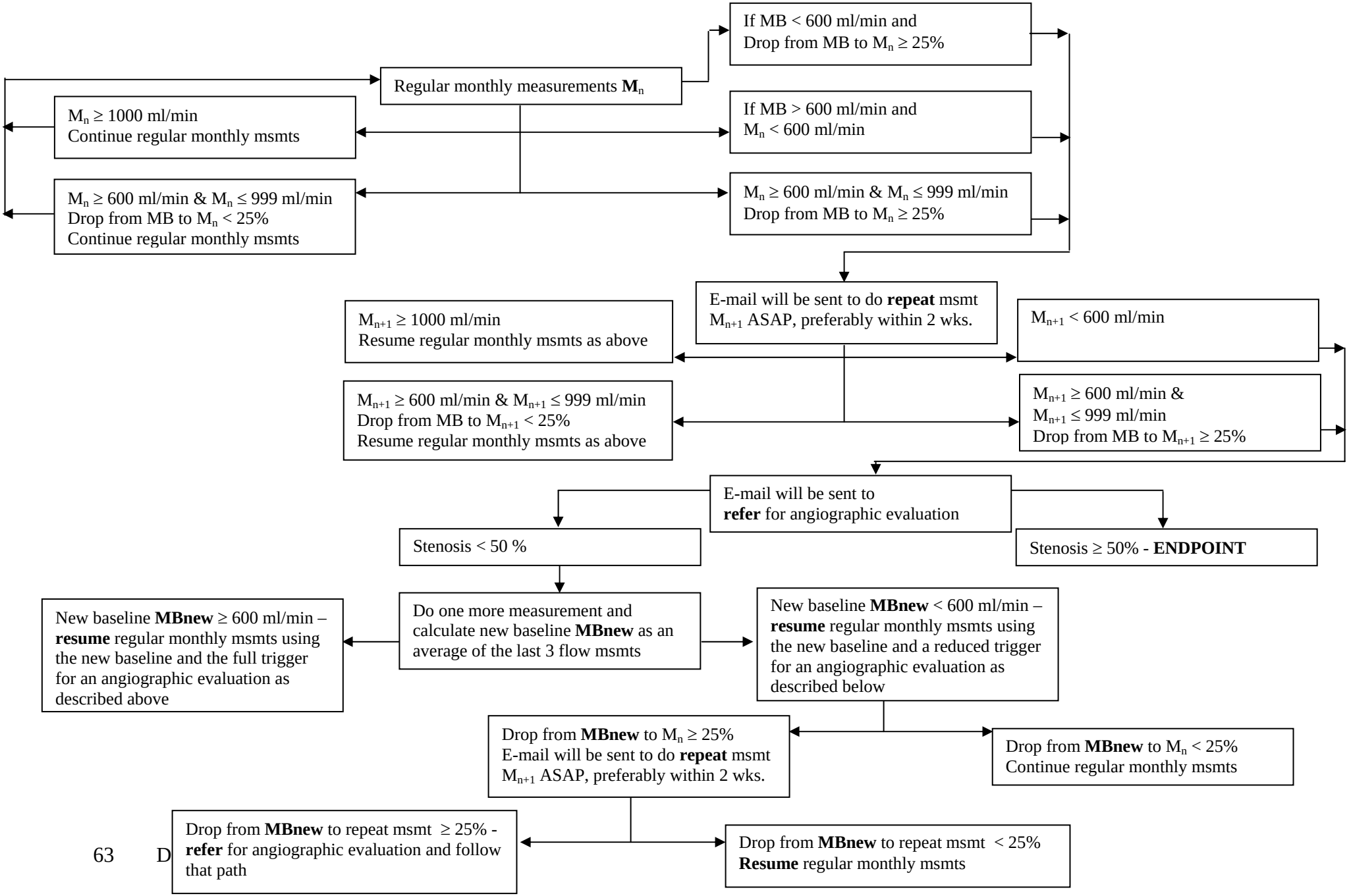


Figure 5.2
Flow Diagram for AVG Surveillance - Regular Monthly Measurements



Setup

- Identify patients for access flow measurements before starting their dialysis treatments.
- Place the arterial (dialyzer inflow) needle into the fistula or graft in the opposite direction to flow in the access device and place the venous return needle in the same direction as flow.
- Begin the following procedure for measuring access recirculation and flow approximately 30 to 60 min after starting dialysis.
- Select a site on the arterial and on the venous dialyzer tubing 5-10 cm (2-4 inches) from the dialysis needle connections.
- Apply a layer of Vaseline to the tubing surface to enable transmission of ultrasound.
- Mount the flow/dilution sensors by clamping them to the tubing at the lubricated sites.
- Plug the two cables from the flow/dilution sensors into the appropriate ports on the monitor.
- Connect the computer and monitor using the 9-pin serial cable and serial port. Either Com 1 or Com 2 may be used but Com 2 will require a RS232 cable adapter.
- Plug the monitor into a hospital grade electrical outlet.
- Turn on the monitor power switch.
- Turn on the computer.
- Once blood or saline is flowing in the tubing, check the “% ultrasound” message on the monitor LCD. If less than 60%, remove the sensors, re-apply Vaseline, and re-mount.

Procedure for measuring access recirculation during dialysis

- Adjust the blood pump rate to the usual dialysis setting (close to maximum) and turn ultrafiltration on (if previously shut off).
- Record the patient's arterial blood pressure and time on the flow sheet.
- Load the Transonic Systems, Inc. software by clicking on the icon "Access Flow and Recirc."
- Select "New Patient" on the Main Menu bar, then either "Select Patient" or "Add Patient" as appropriate from the pull-down menus.
- Enter the requested data (BP, type of access, blood pump and monitor flow readings) and exit.
- Select "Recirculation" on the main menu bar and choose "Record to disk."
- Follow the instructions given on the screen to spread the venous and arterial pressure alarm limits.
- When instructed, release the clamp on the saline bag for a 4 to 5 second count (~20 ml). Do not clamp off the arterial line flow proximally as is done during line flushing. If an error occurs, the computer will prompt for another infusion.
- If the computer screen indicates "no recirculation" stop the computer acquisition and proceed to measure access flow.
- If a percentage recirculation is shown (> 5%), stop the computer acquisition, record the percentage on the flow sheet, and repeat the infusion.

Procedure for measuring access flow

- Stop the blood pump and using universal precautions (gown, gloves, shield/mask) reverse the lines at the needle hubs.
- Set the dialyzer blood pump to 300 ml/min and set the prescribed ultrafiltration rate.
- Record the patient's arterial blood pressure and time on the flow sheet.
- Select "Access Flow" on the main menu bar and choose "Record to disk."
- When instructed, release the clamp on the saline bag for a 4 to 5 second count (20-25 ml). Do not clamp off the arterial line flow proximally as is done during line flushing. If an error occurs, the computer will prompt for another infusion.
- Stop the computer acquisition, record the access flow rate, and repeat the infusion.
- If the difference between the two flows is greater than 10% of the flow, do a third infusion.
- Stop the blood pump and return the lines to their normal (non-reversed) configuration using universal precautions.
- Restore the patient's prescribed blood flow and ultrafiltration rates.
- Record the recirculation percentages (if any) and blood flow rates in the patient's chart.]

5.8 Access management decisions based on access flow measurements

5.8.1 Flow criteria triggering referral for an access fistulogram

A participant should be referred for a diagnostic fistulogram when the monthly mean normalized access flow rate meets either criteria 1 or 2 below and is confirmed by a repeat measurement of access blood flow. The repeat measurement should be done as soon as possible and preferably within 2 weeks. If the repeat measurement does not confirm that one of the criteria have been met for referral for a fistulogram then no fistulogram needs to be ordered and monthly monitoring will continue on schedule until the criteria have been met and confirmed by a repeat measurement. This process is described in Figure 5.2.

1. Mean normalized access flow rate less than 600 ml/min OR
2. If mean access flow is less than 1000 ml/min; a 25% drop in the mean normalized access flow from baseline.
    a. Baseline flow rate is determined by averaging the first two or three measurements of access flow as shown in Figure 5.1.
    b. The monthly change in access flow is determined from the difference between the mean normalized access flow for the month and the baseline access flow rate divided by the baseline access flow rate.

5.8.2 Flow criteria after a negative fistulogram

Failure to find an access stenosis when the flow rate has met the targets for access evaluation defined above may be due to a drop in cardiac output, technical error in making the access flow measurement, or a false negative result with angiography (i.e. missing a stenosis that was actually present). If a participant meets flow criteria and is referred for a fistulogram but the fistulogram is read as less than a 50% stenosis, then the participant will continue to have their access flow rate monitored every 4 weeks on the original schedule. The flow criteria for referral for a new fistulogram will be modified as follows.

1. Establish a new baseline flow rate - A new baseline flow rate will be established using the average of the mean normalized access flow rates from the last two measurements prior to referral for the fistulogram. The change in access flow rate will be determined from this new baseline.
2. If the new baseline is above 600 ml/min - Referral for a repeat fistulogram will be done if either criteria #1 or #2 above are met and confirmed.
3. If the new baseline flow rate is 600 ml/min or less - Referral for a repeat fistulogram will be made solely on the basis of criteria #2. That is a drop in mean normalized access flow greater than a 25% from the new baseline.

6. DATA COLLECTION

6.1 Information collected once at 4 weeks (the first visit) – Complete DAC study form 313 with first study visit.

6.1.1 Date of access surgery

Record the date that this access was created. (Note this must be the same as the date listed on the DAC Study A1 form used for randomization.)

6.1.2 Location and configuration of the graft

1. Location – Is the graft material located in the forearm, upper arm, leg, chest or other location? (Note this must be the same as entered on DAC Study A1 form used for randomization.) Is the graft located on the left or right side?

2. Configuration – Is the graft material straight or looped? In a loop configuration the graft will curve around nearly 180 degrees so that the beginning and end of the graft material are close to the same point usually in the antecubital fossa. In a straight graft, the arterial anastomosis will be more distal in the forearm or arm and the venous insertion of the graft will be more proximal. The graft may bend slightly but does not loop back on itself.

6.1.3 Type of graft

The graft may be made of synthetic material or be a biological allograft, autograft or heterograft.

6.1.4 Surgeon

Record the code for the staff surgeon who was responsible for creating the access. For surgeons in a teaching program the code used will be for the staff surgeon who oversaw the surgery and not the resident surgeon.

6.1.5 Any prior access surgery in same arm or leg

Determine whether the participant ever had a prior access in the same arm or leg and the type and position of the access. This information can best be obtained by asking the participant. Also examine the arm or leg to see if there are any scars on the same arm or leg as the new access other than those used to create the current graft. If the participant does not remember having had a prior access but has other scars on their arm or leg, ask them how they got the other scars. If the study site has an access database then this can be a very useful additional source of information to confirm what prior access surgeries has been performed. If the participant is unable to remember any prior access surgeries but there are unexplained scars on the arm or leg then the participant's medical record should be reviewed to determine what surgeries were performed.

1. Type of prior access – Record whether the access was a fistula or graft or both types were inserted. Many participants will not know the type of access that was placed. This information may be determined by reviewing the access database (if available) or looking at the medical records to find the operative report(s) for the previous access(s). In addition, palpating the old access site(s) may reveal the presence or absence of graft material. If the type of access can not be determined then mark it as unknown.

2. Position of the prior access – Record whether the prior accesses in the same arm or leg were in the forearm, upper arm, both locations or leg. This can be determined from participant history, the location of the previous scars and review of the records as noted above.

6.1.6 Current status of access

Record whether the graft that was the basis for the participant's being enrolled into the study is still patent. For participants who are on dialysis at the time of the visit this is determined by the ability to cannulate the graft and perform hemodialysis. For participants who are not on dialysis at the time of the study visit then patency of the graft is determined by examining the graft by palpation to determine whether a thrill is present in the middle or near the end of the graft where it connects to the vein. If a thrill is not present then the examiner should listen with a stethoscope for a bruit audible in the middle of the graft or near the venous end of the graft.

1. If the graft is not thought to be patent on examination – Talk with participant, review the medical records and if the participant is on hemodialysis, talk with the staff in the dialysis unit to confirm that the graft has failed and determine the date when the graft failed. If it is confirmed that the graft has failed, then DAC form 356 must also be filled out. If it can not be confirmed whether the graft has failed then the participant's dialysis physician should be contacted to determine whether further radiologic studies to evaluate the patency of the graft should be ordered. In the event a diagnostic procedure is done then DAC form 354 will need to be completed. If an access procedure is performed then DAC form 355 must be completed.

4. Teaching the participant to check for an access thrill - The access study coordinator should remind all participants how to feel for a thrill in their access and ask that they check the access daily in the morning and notify study personnel or their dialysis physician if they can not feel the thrill in the access. This is particularly important for participants who are not yet on dialysis, so that an accurate assessment of the date of access thrombosis can be determined.

6.1.7 Date of first cannulation

If the participant has started hemodialysis using the new graft then review the medical records or the dialysis run sheets to determine the date that the access was first cannulated for dialysis.The first use is defined as using two needles in the graft (not just the arterial or venous and perm cath for the other). This should be entered on Form 353 when available.

6.1 Information collected every 4 weeks (all visits)

Complete DAC study forms 314, 315, 333, 334, 351 and 353 with each study visit (See Table 2).

6.2.1 Access recirculation and access blood flow within first 2 hours of dialysis

(See MOP section 5 for access blood flow measurements. Complete DAC form 353.)

6.2.2 Access thrombosis

DAC study form 314.

1. Purpose - Access thrombosis is a primary study endpoint. It is critical to determine whether an access thrombosis has occurred and the date of the thrombosis.

2. Method of assessment – Access thrombosis is operationally defined as the loss of a bruit and thrill in the graft. For participants currently on hemodialysis, this also includes the inability to use the access for hemodialysis. Under most circumstances a subsequent access procedure,

either a fistulogram, Doppler exam, or a surgical evaluation of the access will be used to verify the clinical diagnosis of thrombosis and plan therapy. In the absence of one of these confirmatory procedures, the clinical findings of thrombosis accompanied by abandoning use of the access for hemodialysis will be taken as adequate evidence of thrombosis. The date of thrombosis will be the date that the participant or their caregivers first noted the loss of a bruit and thrill. The access study coordinator should remind all participants to feel for a thrill in their access every morning and to notify study personnel or their dialysis physician if they cannot feel the thrill in the graft.

6.2.3 Access procedure

DAC study forms 314, 354 and 355.

1. Purpose – Any access procedure done to maintain or restore access function is a primary endpoint of the study and must be recorded along with the date of the procedure. It is also important to know what access-related event led to the procedure and this will also be recorded.

2. Method of assessment – At each study visit, the participant and the dialysis staff (if the participant is on hemodialysis) will be asked whether there has been any problem with the access or whether any procedures have been done on the access. If there has been any problem or an access procedure has been performed then the study coordinator must get a complete history from the participant and dialysis nurses (if applicable) about what happened and the indication(s) for any procedures. The study coordinator will then need to review the primary medical records looking for documentation of the access problem(s) and any radiological or surgical procedures done on the access. The results of those records and the findings from any procedures should be recorded on DAC study forms 354 (diagnostic procedure) and 355 (access repair/access replacement procedures). For participants who might be questionable historians it may be necessary to periodically review the dialysis records and medical records to make sure that any procedures have not been overlooked.

3. List of access events that might lead to access evaluation –
   Drop in access flow that meets criteria for access evaluation
   Thrombosis (loss of palpable thrill and bruit)
   High venous pressures
   Inability to achieve the desired blood flow rate on dialysis
   Excessive bleeding post needle removal
   Lower than desired kT/V
   Inability to cannulate access
   Access pain
   Infection
   Aneursym
   Pseudo-aneursym
   Arm swelling
   Ischemia of the distal extremity below the access
   High output state
   Access hemorrhage
   Neurological changes in access arm

4. List of access procedures –

Diagnostic imaging – no intervention done and not a study endpoint

- Fistulogram
- Angiogram
- Venogram
- Other (e.g., MRI)

Interventions – any of these constitute a study endpoint

- Angioplasty – dilation of the stenosis done either by radiology or surgery
- Stent – an expandable coil used to keep the stenosis open
- Thrombolysis – using thrombolytic medications (e.g. TPA) to dissolve clot
- Thrombectomy – removing a clot either during surgery or by interventional radiology
- Surgical debridement tissue around graft site without resection of graft
- Surgical revision of the graft
  - Patch graft - replacement or addition of a patch to the existing graft
  - Interposition graft – resection and replacement of a segment of graft
  - Bypass of prior graft site using new arterial or venous anastomosis
- Surgical creation of a new access site (uses both a new arterial and venous anastomosis)
- Other (rotational myotomy, etc.)

5. Evaluation and reporting the extent of access stenosis – The criteria established for angioplasty is any access stenosis that causes a 50% or greater narrowing of the lumen of the vessel. The optimal technique to evaluate this is an angiogram that uses two orthogonal views of the access (or biplanar angiography if available). It is important to review the records of the angiogram or other diagnostic radiology report to determine the severity of the access stenosis and whether it was assessed using two orthogonal views. The study investigator should request that the radiologist(s) at the study site use two orthogonal views to estimate the extent of access stenosis and to record this estimate in their report. The extent of access stenosis is recorded on DAC form 354 as less than 50%, ≥ 50%, <95% or greater than 95%. Also recorded is whether the evaluation was done using orthogonal views. If this information is not recorded on the radiology report it will be necessary to contact the radiologist to determine this information. In addition, if an angioplasty was performed for a stenosis it is necessary to determine the radiologist's estimate of the degree of residual stenosis after the angioplasty and record this information on DAC form 355.

6. Complex stenosis - The criterion for performing angioplasty is a stenosis that reduces the lumen of the vessel by 50% or more when assessed by orthogonal views. This criterion is well accepted and established for a single focal stenosis. However, the resistance posed by a stenosis is directly proportional to the length of the stenosis and inversely proportional to the fourth power of lumen radius. Hence, the length of a stenosis as well as the reduction in lumen diameter determines the resistance to access flow. For instance, a lumen stenosis of 40% that is 2.1 cm in length would give an equivalent resistance to a 50% luminal stenosis that is 1 cm in length. Thus, it may be clinically appropriate to angioplasty a moderately severe stenosis that does not quite reach 50% reduction in lumen diameter if the length of the stenosis is longer than usual. Similarly, several moderate stenoses in series that individually do not quite reach 50% luminal narrowing may create a resistance that is equivalent to that produced by a single focal 50% stenosis. When such a situation is encountered in a study subject who has been referred for angiography the ultimate decision to angioplasty such a lesion(s) will be left to the interventional radiologist in consultation with the study site

investigator to do what is felt to be in the best interest of the patient. If a procedure is performed then it will be counted as the primary study endpoint.

6.2.4 Problems with needle insertion and use of access clamps

DAC study form 314.

1. Purpose – Problems with needle insertion and the use of access clamps may predispose to access thrombosis.

2. Method of assessment – If the participant is getting regular hemodialysis, ask the participant and their dialysis nurses whether there have been significant problems with needle insertion (or the use of access clamps) within the prior 4 weeks. Also review the dialysis records to determine whether significant problems with needle insertion (or the use of access clamps) have been reported within the prior 4 weeks. Significant problems with needle insertion include the occurrence of any of the following: 1) a major hematoma at the graft site following needle insertion, 2) more than two failed attempts to cannulate the graft or 3) the subjective assessment that multiple needle sticks were frequently needed to cannulate the access. Use of access clamps is defined as the use at any time over the past 4 weeks of mechanical clamps to control bleeding from needle puncture sites at the end of dialysis.

3. Person primarily responsible for doing needle sticks – Record whether the participant or one of the dialysis staff did the majority (over half) of the needle insertions.

6.2.5 Current medications

DAC form 334.

1. Purpose – It is important to track changes in medications throughout the study to determine whether there has been a change in medications that might influence access survival or interact with the study medication to increase the risk of an adverse event.

2. Method of assessment – The participant will be asked to bring their medication bottles including the study medication with them to each study visit. The medications will be reviewed by the study coordinator and recorded on DAC form 334. The participant will also be asked if they have had any change in their medications from the last study visit and whether they are taking any over-the-counter medications or herbal products. The dates of any changes in medications will be noted and recorded on the study form. If the participant lives in a supervised living center where their medications are provided to them or if the dialysis unit keeps an accurate up-to-date record of medications for the subject then these medication lists can be used to obtain this information. It is important if possible to verify the medication list with the participant. If the study participant forgets to bring their medication bottles and no reliable medication list is available then the subject will be asked to bring their bottles on another day for review. If this is not feasible then the study coordinator should contact the subject at home to verify their medications. If the participant is on hemodialysis, then the study coordinator will also need to review the dialysis records to determine whether any medications are also being given in the dialysis unit. Medications commonly given in the dialysis unit include erythropoietin, vitamin D analogues and intravenous iron.

3. Recording the dose of aspirin – The dose of aspirin will be recorded on DAC study form 334. The dose of aspirin taken on a daily basis should be recorded. Do not try to estimate intermittent usage of aspirin or the amount of aspirin in compound over-the-counter medications (e.g., Alka-Seltzer with aspirin or Midol).

4. Medications to avoid – The participant cannot be on any other anticoagulant, antiplatelet agent or nonsteroidal medication other than aspirin while on the study medication (see Table 1).

6.2.6 Compliance with study medication

DAC study form 315.

1. Purpose – The outcome of the study is dependent on participants taking their medications as prescribed. Regular assessment of medication compliance may help to encourage compliance.

2. Method of assessment – The participant will be asked to bring their study medication bottle with them to each study visit to exchange for a new supply of medication. A pill count will be done. If there are a significant number of capsules left in the bottle the study coordinator should inquire whether the participant is taking the medication as prescribed (1 capsule twice a day) and why so many capsules remain in the bottle. If the participant is no longer plans to take the study medication then record this on DAC forms 333 and 336. If the participant reports problems with the study medication then this should be reported on DAC form 333 along with the adverse symptoms experienced by the participant.

6.2.7 Biochemical laboratory tests

DAC form 351.

1. Purpose – Biochemical tests are performed to assess for risk factors that may be related to access failure, to assess the adequacy of dialysis and to monitor for signs of an adverse event (bleeding) from the study medication.

2. Method of assessment – The results of the biochemical studies will be determined by a review of the participant's medical record. The results will be the most recent results done within the last month since the last visit or since the participant was randomized into the study. For subjects on dialysis and most subjects with ESRD who are nearing the need for dialysis these studies will be done monthly on a routine basis. [If they are not done as part of the participant's routine medical care these tests will not be specially requested for the purposes of this study.]

3. List of biochemical tests to collect - The following test results will be recorded.
   - Serum albumin
   - Hemoglobin
   - Hematocrit
   - Pre- and post-dialysis BUN (only for participants on hemodialysis)
   - Serum calcium
   - Serum phosphorus
   - Serum parathyroid hormone (when available, every third month)

6.2.8 Adverse event monitoring

DAC study form 333. May need to complete DAC forms 335, 336, 361, 363, 371 or 372.

1. Purpose – For the study medication to be clinically useful to prevent access stenosis it must have a favorable benefit to risk ratio. Adverse event monitoring is done to assess the risks associated with taking the study medication in this population of patients. An independent data safety and monitoring committee will review the unmasked data as the trial is progressing and will be able to stop the trial if the study medication is found to be associated with excessive risk to the participants.

2. Information to collect – Aggrenox has a low dose of aspirin that will increase the risk of bleeding and may cause gastrointestinal symptoms such as heartburn or ulcers. It is important to monitor for bleeding events, particularly those that are serious, life-threatening or fatal. In addition, it is important to monitor for other side effects even if they are not previously known to be due to the medication, particularly if those adverse events are serious, debilitating, life-threatening or fatal and might be due to the study medication. By definition any hospitalization that lasts more than 24 hours and any death are considered significant adverse events that must be reviewed and the possible contribution of the study medication carefully assessed.

3. Method of assessment – The study coordinator will ask the subject about any adverse events, hospitalizations or transfusions at each study visit. For participants who are questionable historians and are currently on hemodialysis, the dialysis nurse caring for the patient will also be asked whether they are aware of any adverse events, hospitalizations, or transfusions that have occurred in the preceding month. In addition, the participant's dialysis logs will be examined to determine if they missed any dialysis sessions and the participant and dialysis staff will be asked the reason for the absence. Routine surveillance of the participant's medical records looking for unreported adverse events is not required. However, if there is a question about the possibility of an adverse event then the medical records, reports of hospital discharge summaries and any other available sources of information must be reviewed. The study coordinator will ask the subject the following questions at each visit.

a. Ask about any problems with their study medication or new health problems. Describe them. Record the reported symptoms or new health problems on DAC form 333. If the symptoms sound serious and have not been evaluated, contact the subject's nephrologist or primary care physician to follow-up on the evaluation.

b. Ask whether they stopped taking their study medication for any reason since the last study visit. If so, record that on DAC study form 333 along with the reason for discontinuation. Then complete either DAC study form 335 (temporary discontinuation) or DAC study form 336 (permanent discontinuation) as appropriate.

c. Ask about gastrointestinal symptoms such as heartburn, nausea, vomiting, diarrhea, abdominal pain or change in stool color. Record this on DAC study form 333. If the participant is having severe or frequent heartburn (more than once or twice per week), severe abdominal pain, nausea, vomiting, diarrhea, change in appetite, or change in stool color (particularly a black stool color with a foul odor suggestive of melena) then their primary

physician should evaluate them as soon as possible. If the symptoms are potentially serious or intolerable and felt to be due to the study medication then the study medication will need to be discontinued and either DAC study form 335 (temporary discontinuation) or 336 (permanent discontinuation) as appropriate must be filled out. Diarrhea can be due to the study medication and may get better despite continued therapy with the study medication.

d. Ask about any bleeding events or blood transfusions. Bleeding events are categorized as minor, intermediate, major, life-threatening or fatal as defined in MOP, section 4.3.1.

If the participant or dialysis unit nurse knows of any episodes of bleeding or blood transfusions then find out the date(s) of the event(s) and what happened. Specifically, determine whether the subject saw a health care professional about the bleeding, went to an outpatient clinic or emergency room or was hospitalized and whether they received a transfusion as the result of bleeding. If any of these events occurred then the medical records relating to that visit or transfusion must be located and reviewed and DAC study form 363 must be completed. DAC study form 363 is used to determine whether the bleeding event is categorized as intermediate, major, life threatening or fatal as defined above. In addition, if the study medication was either temporarily or permanently discontinued then DAC study form 335 (temporary) or form 336 (permanent), respectively must be completed. Note that the study protocol requires that the study medication be permanently discontinued if the participant suffers a major or life-threatening bleed on the study medication.

If the bleeding is determined to be a minor bleeding event that did not lead to discontinuation of the study drug then only DAC study form 333 needs to be completed. Episodes of minor or intermediate bleeding do not require the permanent discontinuation of study medication.

f. Ask about any hospitalizations. For the purpose of the DAC Studies a "hospitalization" is defined as an event that requires medical attention (including medical care or on-site observation) overnight. If the hospitalization was solely for placement of the study access, this form need not be completed. If the admission date is before the consent was signed, this form need not be completed.. If a participant was hospitalized, find out when the hospitalization occurred and the reason for the hospitalization. In the event of a hospitalization, the study investigator must review the discharge summary or contact the attending physician and complete DAC study form 361 within 2 weeks of the discharge or becoming aware of the hospitalization. If a bleeding event or transfusion occurred, the DAC study form 363 must also be filled out. DAC study form 361 requires that the name and location of the hospital as well as the date(s) of admission and discharge or death and the primary and secondary diagnoses be recorded. In addition, form 361 requires information on whether there was any surgery performed or any diagnostic or interventional procedures done on the vascular access, whether anything lead to prolongation of the hospitalization and whether the study drug was discontinued. Finally, the form requests an assessment of whether the study team remains masked about the study medication and whether the hospitalization was related to the study medication. Hospitalizations are completed through one month after primary endpoint. If the study drug was permanently discontinued, but the primary outcome wasn’t reached yet, hospitalization forms continue to be completed until one month after the primary outcome. SAE’s for hospitalizations are only triggered until 30 days after permanent discontinuation of study drug.

g. Fatal event. If the subject dies while participating in the study then DAC study forms 371 and 372 must be completed. The study personnel must locate all the information related to the death including hospital discharge summary if the subject was hospitalized, and the autopsy report if one was performed. The study investigator is responsible for reviewing this information and filling out form 372 identifying when and where the death occurred, whether an autopsy was performed, the primary and secondary causes of death and whether the investigator believes that the death is related to the study drug. Form 372 must be filed within 6 weeks of the investigator becoming aware of the participant's death. Death forms are completed through one month after primary endpoint. If the study drug was permanently discontinued, but the primary outcome wasn't reached yet, death forms continue to be completed until one month after the primary outcome.

6.3 Information collected every 12 weeks

DAC study form 341.

Quality of life questionnaire – Ask the participant if they would be willing to answer 3 questions about their quality of life. The three questions are:

1. During the PAST 3 MONTHS, how much pain or discomfort have you had due to your dialysis access?
2. During the PAST 3 MONTHS, how much have you worried about your dialysis access?
3. I am satisfied with my life.

A selection of answers is provided on the questionnaire for the participant to choose from.

7. STUDY CLOSEOUT

7.1 Purpose

To obtain information on the secondary outcomes of cumulative graft survival and participant survival for all participants randomized into the study.

7.2 Definition of cumulative graft survival

Cumulative graft survival is the time from randomization until total failure of the access site. Total failure of the access site is defined as the complete cessation of function of the study access that cannot be restored and results in the need to place a new access at a distinctly different site (either a catheter or arteriovenous shunt) to continue hemodialysis.

7.3 When is this information collected

This information can be collected at any time during the study when a participant's graft is known to have irreversibly failed as defined above or when a participant has died. Any participant for whom we do not know whether their access has failed or they have died then this information will need to be determined at the end of the planned 4 years of the study.

7.4 Who collects this information

The study coordinator and study investigator will collect this information.

7.5 Method of assessment

For previously enrolled study participants that have incomplete information on the status of their access or survival, the study coordinator should try to determine this information by directly contacting the person using their most recent contact information. For participants who are still followed for their end stage renal disease at the study site (or were followed there until their death) then the study personnel should be able to verify the status of the graft and the dates of any graft failure or death by reviewing their medical records. If the site keeps an up-to-date access database on all patients then all the necessary information should be readily available from that database. For prior participants who have transferred their care to another site then the study coordinator will need to locate the prior participant or their current dialysis unit or health provider to obtain this information.

Table 1. List of common anticoagulant, antiplatelet and non-steroidal anti-inflammatory medications

Type of medication	Generic name	Trade name	Excluded by study
Anticoagulant	warfarin	Coumadin	Yes
Anticoagulant	heparin	Heparin	Dialysis use okay
Anticoagulant	enoxaparin	Lovenox	Dialysis use okay
Anticoagulant	dalteparin	Fragmin	Dialysis use okay
Anticoagulant	danaparoid	Orgaran	Yes
Antiplatelet	clopiogrel	Plavix	Yes
Antiplatelet	ticlopidine	Ticlid	Yes
Antiplatelet	acetylsalicylic acid	Aspirin – multiple brands	No
Antiplatelet	sulfinpyrazone	Antazone/Anturan	Yes
NSAID	ibuprofen	Motrin	Yes
NSAID	naproxen	Aleve/Naprosyn/Anaprox	Yes
NSAID	indomethicin	Indocin	Yes
NSAID	diflusinal	Dolobid	Yes
NSAID	piroxicam	Feldene	Yes
NSAID	meclofenamate	Meclofenamate	Yes
NSAID	meclofenamic acid	Ponstel	Yes
NSAID	nambumetone	Relafen	Yes
NSAID	ketorolac	Toradol	Yes
NSAID	ketoprofen	Orudis	Yes
NSAID	fenoprofen	Nalfon	Yes
NSAID	etodolac	Lodine	Yes
NSAID	diclofenac	Voltaren/Arthrotec	Yes
NSAID	sulindac	Clinoril	Yes
NSAID	tolmetin	Tolectin	Yes
NSAID	oxaprozin	Daypro	Yes
NSAID	celecoxib	Celebrex	Yes
NSAID	rofecoxib	Vioxx	Yes
NSAID	valdecoxib	Bextra	Yes

NSAID, nonsteroidal anti-inflammatory drug

List of NSAIDs in Micromedix

aceclofenac
acemetacin
alclofenac
amtolmetin
azapropazone
benoxaprofen
bromfenac
bufexamac
carprofen
celecoxib
clonixin
dexibuprofen
dexketoprofen
diclofenac
diclofenac/hyaluronic acid
diflunisal
dipyrone
droxicam
etodolac
etofenamate
felbinac
fenbufen
fenoprofen
fentiazac
floctafenine
flufenamic acid
flurbiprofen
ibuprofen
indomethacin
indoprofen
isoxicam
ketoprofen
ketorolac
lornoxicam
loxoprofen
meclofenamate
mefenamic acid
meloxicam
morniflumate
nabumetone
naproxen
niflumic acid
nimesulide
oxaprozin
parecoxib
phenylbutazone
piketoprofen
pirazolac
piroxicam
pirprofen

propyphenazone
proquazone
rofecoxib
sulindac
suprofen
tenidap
tenoxicam
tiaprofenic acid
tolmetin
valdecoxib
zomepirac

Table 2: Graft Baseline Forms - Forms Completion Schedule

	Forms						
Time							
Prior to Randomization	311	322	324	331	333	341	351
	X	X	X	X	X	X	X

Fax signed consent with patient ID, namecode and study name to the DCC with signature blocked out. The patient must be randomized within 90 days of the date the consent is signed, or you will need to get a new consent.

If the patient has already consented and you know that he/she is ineligible, complete Forms 311 and 331. You do not fill out a drop-out form.

If labs and forms are 45 days old, redo baseline forms except for Form 322, 331 and 341 (which should be reviewed for accuracy). These forms will have to be updated after 90 days.

Forms 311, 322, 324, 331, 333, and 341 may be entered in any order. When results for the blood work are received, the Local Biochemistry Laboratory Form 351 may be entered.

After the forms are entered, run the on-line eligibility report. It will indicate if the DCC has received the consent, if the patient is eligible, and the last day the patient can be randomized without having to get additional data.

Other forms that are completed as needed are: Form 360 (Hospitalization Notification), Form 361 (Clinical Center Hospitalization), Form 363 (Transfusion/Bleeding Episodes), Form 365 (Life Threatening Event), Form 366 (Birth Defect Event), Form 371 (Clinical Center Death Notification) and Form 372 (Clinical Center Death Review).

Complete Form 312 (Graft Study Dropout Form) if the patient will not be randomized.

Table 3: Graft Follow-Up - Forms Completion Schedule

Forms									
	313	314	315	316	333	334	341	351	353
Time									
At Randomization			X						
Month 1	X	X		X	X	X		X	If access used for dialysis
Month 2 through first follow-up visit after primary end-point		X		X	X	X		X	X
Quarterly Follow-up (months 3, 6, 9, 12)							X		
30 Days after drug discontinued: safety call					X				

Other forms as needed:

If drug is discontinued at any time after randomization: Form 335 (Temporary Discontinuation of Therapy) or Form 336 (Permanent Discontinuation of Therapy). If the patient was prescribed a reduced dose of the study drug, complete Form 317.

At monthly follow-ups through first follow-up after primary endpoint, if needed:

Form 354 (Diagnostic Procedure [Fistulogram, Angiogram, Venogram]), Form 355 (Access Repair/Access Event Procedure [Angioplasty and other procedures]), Form 356 (Site Failure, Thrombosis [End Point]), Form 360 (Clinical Center Hospitalization Notification), Form 361 (Clinical Center Hospitalization), Form 363 (Transfusion/Bleeding Episodes), Form 364 (Persistent Disability/Incapacity-only after at least 3 months), Form 365 (Life Threatening Event), Form 366 (Birth Defect Event), Form 371 (Clinical Center Death Notification), Form 372 (Clinical Center Death Review), and Form 382 (Patient Transfer).

At the 30-day safety call after the drug is discontinued, if needed:

Forms 354, 355, 356, 360, 361, 363, 364, 365, 366, 371, 372

After study participation ends:

Until the end of the study, complete the Form 390 (Annual Vital Status Check).

Visit/Sequence Numbering:

When filling out forms that have visit numbers and/or visit sequence numbers, use the graft appointment schedule (found under "Reports" in the main menu) to determine the visit number. The visit sequence number within any given visit number is incremented from "1" on as needed.

Table 4: DAC Drug Distribution Sites

Center 1 - Boston University Medical Center
Closet 11: Boston Medical Center
Closet 12: Boston Veterans Administration Medical Center
Closet 14: Brockton Dialysis Center
Closet 16: Taunton Kidney Center
Closet 17: Baystate

Center 2 - Duke University Medical Center
Closet 21: Duke University Medical Center

Center 3 - University of Iowa
Closet 31: University of Iowa
Closet 34: Nephrology Associates
Closet 37: VA Medical Center

Center 4 - Maine Medical Center
Closet 41: Maine Medical Center Research Institute

Center 5 - University of Texas Southwestern
Closet 51: UT Southwestern University at Dallas

Center 6 - University of Alabama at Birmingham
Closet 61: University of Alabama at Birmingham

Center 7 - Washington University
Closet 71: Chromalloy American Kidney Center

Center 8 - Vanderbilt Medical Center
Close 81: Vanderbilt Medical Center

Center 9 - Wake Forest University Baptist Medical Center
Closet 91: Wake Forest University Baptist Medical Center

Center 10 – Charleston Area Medical Center
Closet 101: Charleston Area Medical Center

Center 11 – Emory University
Closet 111: Emory University

Center 12 – St. Louis University
Closet 121: St. Louis University

Center 13 – Tyler Nephrology Associates
Closet 131: Tyler Nephrology Assciates

Center 14 – Vascular Surgery Associates
Closet 141: Vascular Surgery Associates