Dialysis Access Consortium (DAC)

Manual of Operations

Fistula Study

Dialysis Access Consortium
Manual of Operations
Fistula Study
(10/13/05)

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. An example of a letter that could be sent to prospective study participants is also enclosed (Figure).

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 synthetic vascular access graft in the upper extremity 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 301 (screening form)
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 surgery. Enrollment must be completed no later than 1 calendar day 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.

3. FISTULA FULL-SCALE STUDY: DESIGN, VISITS, MEASUREMENTS, ADVERSE EVENTS

3.1. Full-Scale study design summary

Title

Clopidogrel Prevention of Early AV Fistula Thrombosis

Objective

Evaluate the efficacy of clopidogrel in preventing the early failure of native AV fistulae for hemodialysis

Type of Study

Randomized, double-blind, placebo-controlled
Multicenter: 7 centers

Treatment Groups

Clopidogrel
Placebo

Stratification

Clinical Center
Fistula Location: forearm vs upper arm

Outcomes

Primary:
- Fistula patency at six weeks

Secondary:
- Fistula suitability for dialysis
- Fistula suitability for dialysis without radiological or surgical modification

Blinding:
- Patients and study personnel masked to treatment assignment
- Data and Safety Monitoring Board (DSMB) masked to treatment assignment

3.2. Treatment general information: full-scale study

3.2.1 Treatment Contents

Treatments:

Clopidogrel
Placebo

Clopidogrel

Clopidogrel (Plavix), Sanofi / Bristol-Myers Squibb is a thienopyridine derivative that selectively and specifically interferes with ADP-mediated platelet activation causing an irreversible, non-competitive inhibition of platelet function. Release of platelet granule constituents, platelet-platelet

interactions, and platelet adhesion to the endothelium and atheromatous plaque are all inhibited by the drug.

Placebo

The placebo consists of a tablet containing inactive ingredients.

3.2.2. Treatment dose and administration: Full-Scale Study

Clopidogrel dose

The first dose is clopidogrel 300 mg (4 pills) then
75 mg (1 pill) by mouth once per day

Placebo dose

The first dose is placebo (4 pills) then
One pill by mouth once per day

Measures to ensure blinding

Appearance and packaging of clopidogrel and placebo will be identical
In the event of a major or life-threatening bleeding episode or in the event that emergent surgery is required study drug will be discontinued. Treatment assignment will not be revealed unless the physicians caring for the patient feel that platelet transfusion is indicated if the patient was receiving clopidogrel.

3.2.3. Discontinuation of treatment: Full-Scale Study

Temporary discontinuation of study drug

The study drug may be temporarily discontinued if either of the following events occur:

Intermediate bleed (see section 4.4.1. for definition)
Surgery or invasive procedure

The decision to discontinue study drug and the length of cessation of study drug should be made by the study physician together with the physician(s) caring for the patient. The Data Safety and Monitoring Board/External Advisory Committee (DSMB/EAC) will review the rates at which medications are discontinued. Do not give drug after the 6 week drug administration period even if some pills were missed.

Permanent discontinuation of study drug

1. Major or life-threatening bleed (see section 4.4.1. for definitions)
2. Allergic reaction
3. Development of a medical condition that requires use of clopidogrel, warfarin, heparin (other than during hemodialysis), dipyridamole, sulfinpyrazone, aspirin, non-steroidal anti-inflammatory agents, or other anti-thrombotic agents.
4. Development of medical condition that precludes use of anti-platelet agent
5. Pregnancy
6. Study physician believes that discontinuation is in the patient's best interest
7. Patient's request

8. Discontinuation of hemodialysis because of renal transplantation, recovery of renal function, change in dialysis modality
9. Fistula thrombosis. Thrombosis must be confirmed by vascular surgeon or nephrologist. If patency is restored surgically or by an interventional radiology procedure the study medication should be discontinued, but participation in the study will continue until the ascertainment of fistula suitability for dialysis.
10. Withdrawal from the study

In the event of either temporary or permanent discontinuation of study drug, the patient should be followed and data collected until requirements for study completion are met. Form 335 or 336 should be completed.

3.2.4. Events that do not require discontinuation of treatment: Full-Scale Study

The following events do not require discontinuation of the study medication:

Hypertension
Anemia
Gastrointestinal distress
Minor bleeding events
Intermediate bleeding events
Infection

3.2.5. Unmasking treatment assignment: Full-Scale Study

All clinical personnel and patients are masked to treatment assignments during the trial. Treatment assignments will not be unmasked if the study drug is discontinued during study participation unless this information is required for medical management (e.g., to determine whether platelet transfusions are required to stop or prevent bleeding).

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 unmask 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) in the Fistula Study

   *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.

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) in the Fistula Study
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.

3.2.6. Concomitant medications: Full-Scale Study

Patients should not receive the following medications during the six-week study drug administration period:

Aspirin
Non-steroidal anti-inflammatory drugs (NSAIDs)
Dipyridamole
Sulfinpyrazone
Warfarin
Other anti-thrombotic agents

Heparin during dialysis treatments is allowed.
Analgesic medications that do not contain aspirin or NSAIDs are allowed.

If proscribed agents are medically indicated during the six-week study drug administration period, study medication should be discontinued (see section 3.2.3), and the patient should continue to be followed and data collected until requirements for study completion are met. Form 335 or 336 should be completed if study medication is discontinued.

3.2.7. Events that require withdrawal from the study: Full-Scale Study

A patient will be withdrawn from the study for the following reasons:

The patient leaves the participating dialysis unit and cannot be followed in another dialysis unit.
The patient is judged lost to follow-up after repeated attempts to contact have failed.
Withdrawal of consent.
Death.

3.2.8. Surgery or other invasive procedures during study drug administration period: Full-Scale Study

Elective procedures should be delayed until 7 days after the end of the study drug administration period if possible.
If an elective procedure with a bleeding risk is not delayed until after the study drug administration period, 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.

If emergent surgery with a risk for bleeding is required(e.g., neurosurgery, hip replacement, abdominal surgery), study medication should be discontinued and consideration should be given to revealing the medication code and administering platelet transfusion if the patient has been receiving active drug.
Form 335 should be completed if study drug is temporarily discontinued.
Form 336 should be completed if study drug is permanently discontinued.

3.2.9. Fistula Use and Procedures: Full-Scale Study

Decisions about when to use the new fistula should be made by the patient's treating physician(s) and not by study personnel.

Decisions to perform fistula procedures or create a new dialysis access should be made by the patient's treating physician(s) and not by study personnel.

3.3 Full-scale study visits, patient contacts, and outcome assessments

3.3.1. Screening / Baseline visit: Full-Scale Study purpose

Obtain informed consent
Evaluate eligibility
Review treatment procedures and schedule

Time frame

Consent process / signature: must be obtained between 90 days prior to and one calendar day following fistula creation surgery.
Laboratory studies and eligibility review: must occur between 45 days prior to and one calendar day following fistula creation surgery.

Procedures

Obtain informed consent (patient and study personnel signatures and date)
Collect the following:
- --Baseline medical history
- --Demographics
- --Access history
- --Dialysis history
- --Height and weight
- --Blood pressure
- --Laboratory data / specimens

Record current medications
Quality of Life assessment
Instruct patients on aspirin to discontinue aspirin 7 days prior to fistula creation surgery
Provide patient with study personnel contact information

Laboratory Specimens

CBC, calcium, phosphorus, PTH, albumin if not already available.
The CBC values must be obtained between 45 days prior to and one calendar day following the date of fistula creation.
Specimen for blood and DNA repository (See Section 3.4.4)

Forms completed (See Table 1)

301 Fistula Screening
302 Fistula Baseline Dropout (if necessary)
322 Patient Family, Employment and Income
324 Baseline Medication
331 Demographics, Comorbidity, and Dialysis History
333 Visit
341 Quality of Life Assessment
351 Local Biochemistry Laboratory Data
395 Mailing of Blood/DNA Specimen

Informed Consent Form procedures

Retain original in Clinical Center file
Provide patient with copy
Submit copy to patient's medical record(s)
Fax to DCC a copy of the signature page with patient name "whited out", ID and name code, and study name

Quality of Life Assessment

Consists of 3 questions with multiple choice answers
Can be self-administered or administered by study personnel

3.3.2. Randomization visit / contact: Full-Scale Study

Purpose

Determine that a native fistula was created
Randomize to treatment group
Deliver study medication to patient

Time Frame

Within 1 calendar day after surgery

Procedures

Confirm that a native fistula was created. This confirmation can be made directly by study personnel or through communication with the vascular surgeon or other individuals deemed appropriate by the investigator. **If a fistula was not created or the surgeon reports that the fistula has thrombosed the patient should not be randomized to treatment group. You must also check that the patient meets all eligibility criteria before randomization (i.e., aspirin has been discontinued for 7 days prior to fistula creation surgery).**
Randomize patient using on-line system.
Deliver study drug to subject. Study drug delivery can be performed directly by study personnel or by individuals designated by the investigator (e.g., investigational pharmacist).
Provide instructions to patient regarding: study drug administration, study personnel contact information, and adverse event reporting.
Contact patient one day after randomization to remind him/her to take study medication.

Forms Completed (See Table 2)

A2 Fistula Study Randomization On-Line Application
302 Baseline Drop-Out Form (if necessary)
306 Pill Dispensing Form

Note: If there was a protocol violation and the wrong type of vascular access was randomized (fistula study patient received a graft), 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.

Instructions to Patient

Take the first dose of study drug (4 pills) and then one pill by mouth per day for six weeks
Avoid non-steroidal anti-inflammatory agents, aspirin, warfarin, clopidogrel, and dipyridamole for the next six weeks
Inform the study team if your physicians start you on any new medications during the next six weeks
Contact the study team if you have any type of bleeding, dark stool, abdominal discomfort, heartburn, rash, or any other new symptoms
Bring the medication bottle with you to your six week study visit

3.3.3. Day 1, Two-week, and Four-week telephone contacts: Full-Scale Study

Day 1 Telephone Contact

The patient should be contacted by telephone (or in person) one day after study drug delivery to:
remind him/her to take the study medication as directed.
Be sure he/she knows how to contact study personnel
Document this on Form 304

Two-Week Telephone Contact

The patient should be contacted by telephone (or in person) two weeks after fistula creation to:
Remind him/her to continue taking the study medication
Find out about any intercurrent medical events
Find out about any new medications started
Find out about any difficulty tolerating study medication
Find out about any access procedures
Document this on Form 304

Four-Week Telephone Contact

The patient should be contacted by telephone (or in person) four weeks after fistula creation to:
Remind him/her to continue taking the study medication
Find out about any intercurrent medical events
Find out about any new medications started
Find out about any difficulty tolerating study medication
Find out about any access procedures
Remind him/her of the six week study visit
Document this on Form 304

3.3.4. Six-Week visit: Full-Scale Study

Purpose

Primary outcome assessment
Secondary outcome assessment (if relevant)

Adverse event assessment
Study drug compliance assessment
Evaluation of blinding

Time Frame

Six weeks after fistula creation surgery (recommended window is 39 – 66 days after fistula creation surgery)

Procedures

Fistula patency assessment (see section 3.3.5)
Fistula anatomy assessment – to be obtained from operative note or discussion with surgeon. This information can be obtained at the time of surgery but will be entered on data form at the six week visit.
Record current medications
Record all intercurrent/adverse events
Record date of initiation of dialysis via fistula if applicable
Record any procedures on fistula since creation
Perform study drug pill count
Record study team' s impression of treatment group assignment
Quality of Life assessment
Instruct patients on aspirin prior to randomization to resume aspirin

Forms completed

304 Fistula Patency
333 Visit
334 Medication Tracking
335 Temporary Discontinuation of Therapy (if necessary)
336 Permanent Discontinuation of Therapy (if necessary)
341 Quality of Life Assessment
352 Access Repair/Access Event Procedure (if necessary)
360 Clinical Center Hospitalization Notification (if necessary)
361 Clinical Center Hospitalization (if necessary)
363 Transfusion/Bleeding (if necessary)
364 Persistent Disability/Incapacity Form (if necessary only after at least three months)
365 Life Threatening Event (if necessary)
366 Birth Defect Event (if necessary)
371 Clinical Center Death Notification (if necessary)
372 Clinical Center Death Review (if necessary)

Quality of Life Assessment

Consists of 3 questions with multiple choice answers
Can be self-administered or administered by study personnel

3.3.5. Fistula patency assessment (Form 304): Full-Scale Study

The primary outcome is fistula patency, defined as absence of thrombosis within six weeks after fistula creation. Fistula patency will be determined by physical examination of the fistula performed by a trained study team member after training and evaluation by the study investigator.

The fistula will be classified as patent if a bruit is present throughout systole and diastole. A tourniquet should NOT be applied during fistula patency assessment.

The bruit evaluation should be made with a stethoscope placed over the vein at least 8 centimeters proximal to the arteriovenous anastomosis. The requirement for an 8 cm or greater distance from the estimated location of the anastomosis is to minimize the likelihood of misclassification of thrombosed fistula as patent because of a bruit resulting from turbulence at the anastomosis.

The fistula patency outcome will be ascertained at 6 weeks in all patients except those who discontinued study drug because of fistula thrombosis prior to six weeks. Fistula patency assessment should be performed even if study drug was discontinued prior to six weeks for a reason other than thrombosis. The recommended window for assessment is 39 to 66 days after fistula creation surgery (42 days after surgery is optimal).

In a quality control subset of patients, the outcome will be independently assessed by at least one trained member of the study team and a second person in order to evaluate the quality of the patency outcome determinations.

To allow patients with fistula thrombosis and no restoration of patency to complete study participation within 30 days of study drug discontinuation, the fistula patency outcome assessment may be completed at any time within the 30 days following study drug discontinuation.

Fistula patency data should be entered on Form 304.

3.3.6. Monthly data collection after Six-Week Visit

Contact will be made with the patient, their dialysis facility, and/or physicians on a monthly basis until study completion in order to obtain the following information:

Bleeding events during the 30 days following the end of study drug administration period
Hospitalizations during the 30 days following the end of study drug administration period
Death forms 371 and 372 are completed through suitability assessment. If the fistula is abandoned before the six-week visit, the death should be reported in the same way as SAE's (i.e., report a death that occurs within 30 days following discontinuation of study drug)
Date of first dialysis (for patients not on dialysis at time of randomization)
Date of first cannulation of fistula
Date at which fistula is used for four weeks of consecutive dialysis treatments
Procedures performed on fistula (angioplasty, surgical revision, thrombectomy, ligation of draining veins, ligation of fistula, conversion to graft)
Fistula suitability for dialysis assessment (see section 3.3.7.)

Forms completed (if indicated)

361	Clinical Center Hospitalization (if necessary and only until 30 days after six week visit)
363	Transfusion/Bleeding (if necessary and only until 30 days after six week visit)
371	Clinical Center Death Notification (if necessary)
305	Fistula Suitability (at appropriate time; see section 3.3.7.)

3.3.7. Fistula suitability for dialysis assessment (Form 305)

Data for determination of fistula suitability will be obtained from dialysis sessions:

--12 consecutive dialysis sessions that actually occurred should be reported.

--For **prevalent** patients (i.e., patients who started dialysis before fistula creation surgery): Fistula suitability outcome ascertainment will begin 120 days after creation of the fistula. The suitability assessment will be based on the 12 consecutive dialysis sessions starting with the *first session of fistula* use between 120 and 150 days after fistula creation. If the fistula has not been used by 150 days, it should be considered unsuitable.

--For **incident** patients (i.e., patients not yet on dialysis at the time of fistula creation surgery): Fistula suitability ascertainment will begin 120 days after fistula creation if *dialysis is*

initiated within 120 days of fistula creation, or at the onset of initiation of dialysis if dialysis is initiated more than 120 days after fistula creation.
If dialysis is initiated within 120 days of fistula creation, the suitability assessment will be based on the 12 consecutive dialysis sessions starting with the first session of fistula use between 120 and 150 days after creation, and will be considered unsuitable if the fistula has not been used for dialysis by 150 days (i.e., another type of access was used).
If dialysis is initiated more than 120 days after fistula creation, the suitability will end with the 12th consecutive dialysis session that takes place (starting with the first session of dialysis), or by 60 days after initiation of dialysis, whichever comes earlier.

Dialysis Machine Blood Flow Data

--Dialysis machine blood flow data should be obtained for each dialysis session during the relevant assessment period as described above.

--The blood flow data should be obtained from dialysis unit records (e.g., run sheets or computer printouts).

--The minimum and mean dialysis machine blood flow for each session during the period between the first hour and the last 15 minutes of dialysis should be recorded on Form 305.

Fistula Modification Data

--Fistula modification data (procedures performed on fistula) should be obtained as part of the monthly data collection (see section 3.3.6.) and entered on Form 352 at the time of fistula suitability for dialysis assessment.

Form 305 should be filled out:

--If the fistula is abandoned between 6 weeks and 150 days after fistula surgery, Form 305 should be completed at the time it is abandoned. Abandonment should be confirmed with the P.I.

--If the fistula was altered (i.e., catheter or piece of graft was used with the fistula), suitability can be assessed as long as Q. 8 and 9 (was a different artery used?, was a different vein used?) on Form 352 are both answered as "no".

--For all other cases, Form 305 should be completed following the assessment periods described above.

3.3.8. Close-Out Visit: Full-Scale Study

Purpose

Assess secondary outcomes
Assess adverse events
Inform patient that participation in study has ended

Time Frame

Visit should occur as soon as the Fistula Suitability for Dialysis assessment has been performed (see section 3.3.7.):
For patients who do not start hemodialysis while the study is ongoing, the close-out visit should occur at completion of the study and the fistula suitability assessment will not be performed.

Procedures

Complete fistula suitability assessment
Quality of Life assessment
Inform patient that participation in study has ended

Forms

305 Fistula Suitability
341 Quality of Life Assessment
390 Annual check on Vital Status (Completed before the end of the Study)

Enrollment In Competing Studies

A patient may be enrolled in a competing study after the secondary outcome for the fistula study has been ascertained.

3.4.1. Bleeding event categorization: Full-Scale Study

Bleeding events are categorized as minor, intermediate, major, life-threatening and fatal as according to the Protocol section 4.4.1.
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.

3.4.2. Bleeding event management: Full-Scale Study

Bleeding events should be managed as described in Protocol section 4.4.1.

3.4.3. Adverse event reporting

Definition of Serious Adverse Events

Inpatient hospitalizations during baseline, study drug administration period or 30 days thereafter
A persistent or significant disability/incapacity (Form 364)
A life-threatening adverse experience (Form 365)
A congenital anomaly or birth defect (Form 366)
Death at any time during study participation (Form 371)

Adverse Event Reporting

A Serious Adverse Event (SAE) report will be triggered whenever one of the forms 360, 361, 364, 365, 366, or 372 is submitted. The first page of the SAE report will be emailed automatically to the Clinical Center and the DCC. If the event is considered unexpected and drug related, the first page will also be emailed to NIH. In addition, the Clinical Center personnel needs to fill out and enter a second page of the report and fax the whole report to the DCC (for an SAE which is either expected or not related to the study medication), or to the DCC, NIH, their local IRB (if the SAE is related to the study medication and unexpected).

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 9

Michael Rocco, M.D.
Pirouz Daeihagh, M.D.

3.4.4 Collection of Specimens 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 3.4.5, 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.

3.4.5 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.

4. FISTULA TEMPLATE CONSENT

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	**Clopidogrel Prevention of Early AV Fistula Thrombosis**	
Sponsor:	National Institutes of Health/NIDDK	
Investigators:	Telephone No. (regular office hours)	Telephone No. (other times)
[Names here]		

INVITATION: Because you have chronic renal failure and will be undergoing creation of a native arteriovenous fistula for hemodialysis, you may be eligible to participate in this research clinical trial. 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 more than 1,400 patients on hemodialysis in this study in the United States.

PURPOSE: Arteriovenous fistulas provide the most stable access to the bloodstream for patients on hemodialysis. Unfortunately, many hemodialysis patients who have arteriovenous fistulas placed experience problems with the fistula due to clotting. The purpose of this study is to evaluate the use of the drug Plavix (clopidogrel) compared to a placebo (inactive substance) in patients with newly-placed arteriovenous fistulas to improve vascular access for hemodialysis.

PROCEDURES: Your participation in this study will likely last five months. However, if you have not started dialysis by then, your participation will end one month after you start dialysis or when the study ends (up to four years). Hospitalization and mortality data will be obtained using national databases while the study is on-going and for up to five years after the study has ended. In the study, patients who are scheduled to receive a arteriovenous fistula for the first time will be randomly selected (like drawing straws) to receive clopidogrel or placebo (inactive substance). Clopidogrel may prevent the clotting of the fistula and improve the chances of you having a better fistula on dialysis. 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, your medical history will be reviewed and you will undergo a physical examination to determine whether you are eligible to participate in the study. In addition, lab test results in your medical records from your primary renal clinic will be reviewed to determine your eligibility. You will have your blood pressure measured and you may need to have blood drawn (1 – 2 tablespoons) for certain laboratory tests. Most of these are blood tests that you would have prior to surgery even if you were not in the study. The first study visit will take 1-2 hours.

Randomization: If Dr. [names] believes that you qualify to participate in the study, you will receive either the medication clopidogrel or a placebo (an inactive substance). Half of the participants will receive clopidogrel; 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, 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 a supply of clopidogrel 75mg tablets or identical-appearing placebo pills to take four pills within one calendar day following fistula creation surgery, and after that, one pill daily. The drug will be taken orally once a day with water after proper instruction from the study staff. You will only continue taking the medication for six weeks. Then, the research team will continue to follow you by the standard plan of care for patients with arteriovenous fistulas. All unused drug and empty bottles must be returned to the research staff at the end of the six-week medication part of the study. If at any time Dr. [name] 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 fistulas will be offered.

During the study, the research staff will review your routine lab results and clinical information from your dialysis unit or renal clinic. Every two weeks during the medication part of the study, the research team will contact you and discuss your drug compliance. Your second study visit will take place when you finish taking the study medication (six weeks after your fistula is created). At this visit, your fistula will be examined to see if it has blood flow. The examination consists of listening to the fistula with a stethoscope. At this visit any unusual symptoms you experienced during the previous six weeks will be reviewed. The study nurse or study physician will conduct a Quality of Life Questionnaire. This will consist of 3 questions about how you have been feeling since your fistula was created. This study visit will take approximately one hour. Your nephrologist and/or vascular surgeon will decide when to start using your fistula for dialysis. Their decision will be based on when you need to start dialysis (if you are not already getting dialysis treatments), and on whether the fistula appears ready to be used. It usually takes 6-12 weeks for a fistula to be ready for use. Your participation in the study will not affect the decision about when to use the fistula.

Your third study visit will take place 5 months after fistula creation if you have already started dialysis, or at the end of the first month of dialysis if you have not started dialysis within 4 months of fistula creation. At this visit a second Quality of Life Questionnaire will be conducted. This will consist of 3 questions about how you have been feeling during the previous 3 months. Once your fistula is being used, information about how well it is functioning will be collected as part of the study. The information will include the dialysis machine blood flow rate at your dialysis sessions. Your participation in the study will end at the time of the third study visit, unless you have not started dialysis by then. In this case, your participation will end one month after you start dialysis or when the entire study has been completed.

Typically after several months your fistula should be ready for use for hemodialysis. However, you and your arteriovenous fistula will be monitored by your physician and the research team using standard practices before the fistula is used for dialysis. If your fistula should clot, the research team will work with you, your nephrologist, and your surgeon to attempt to save the fistula. In most instances, surgery will be required to re-create vascular access. This may be placement of a new fistula, modification of your existing fistula, or placement of a catheter. The treatment chosen will depend on your anticipated need for dialysis, your physicians, and the blood vessels in your arm. This is our standard of care.

The results of the study are also monitored by a panel of experts called the Data Safety and Monitoring Board. 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: Clopidogrel is approved by the U.S. Food and Drug Administration (FDA) for use to help prevent recurrent stroke. Clopidogrel is a prescription medication that is frequently used for vascular disease. It has not yet been approved for prevention of clotting in arteriovenous fistulas.

POSSIBLE RISKS: Clopidogrel: This medication may help your medical problem but also cause side effects. It is not possible to predict whether you will experience some or none of the side effects listed below. Information about the possible side effects of treatment with clopidogrel 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 clopidogrel 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. Some patients on clopidogrel may have problems with bleeding. In studies where similar medications were used in patients with kidney failure and fistulas, the rates of bleeding were 0-19%. However, none of these studies showed higher bleeding rates for patients given the clopidogrel-like medications than in placebo-treated patients. In a large study of nearly 20,000 patients without kidney failure, clopidogrel was determined to be at least as safe as medium-dose aspirin. In order to minimize the possibility of side effects you will not be eligible to participate in the study if you have bleeding disorders, if you have had a recent serious bleeding episode, or if you have liver disease.

Interaction with other medications that affect platelet function, or blood clotting. Medications that increase your likelihood of bleeding may interfere with the interpretation of the study or may increase your risk during the study. For the six-week duration that you are taking the clopidogrel or placebo, you will be asked to discontinue aspirin or any similar medication until the end of the six week study drug administration period. You will be permitted to resume aspirin thereafter. If the research team and your physician determine that you require aspirin treatment or other blood thinners, you will not be eligible to participate in the study.

Risks to an unborn child or a breast-fed infant. It is not known whether clopidogrel may harm an embryo or fetus or an infant who is breast-feeding. It is not known whether treatment with clopidogrel 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 the placebo, you will not receive the active medication.

Blood samples. For blood samples taken during the study, 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 clopidogrel 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.
- 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 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: You may increase your quality of life by lowering the chance of developing a clot in your arteriovenous fistula by taking part in this study. It is possible that you may not benefit from participation 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: You do not have to participate in this research study to receive care for your medical problem. Alternative care includes standard care patients get with arteriovenous fistulas. If you decide to participate in research, but later change your mind, you may receive the alternative care.

THE DOCTOR'S DECISION TO STOP YOUR PARTICIPATION: Your doctor or the sponsor may stop your participation in this research without your permission under any one of the follow conditions:

- Your medical problems remain unchanged or become worse.
- Side effects become very severe.
- Your doctor believes that participation in the study is not safe for you.
- Your doctor believes that other treatment may be more helpful.
- 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: The sponsor will pay the expenses for all examinations/tests/blood work/study medication that are part of this study. Other expenses resulting from standard care for your medical problems are your responsibility (or the responsibility of your insurance provider or government program). [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 which

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. You may be taken out of the research study if: 1) the investigator decides that continuing in the study would be harmful to you, 2) you need treatment not allowed on this study, 3) you become pregnant, or 4) the study is ended by the sponsoring agency.

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 and the study's Data Coordinating Center. 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. The records of your participation in this research may be reviewed by members and staff of the IRB at this medical center. You may be contacted by a representative of the Board 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: Compensation for a physical injury resulting from participation in this research is not available from the [name of institution]. However, you retain your legal rights during your participation in this research.

YOUR QUESTIONS: The study staff at [name of institution] 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 [phone # of IRB].

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	_____ 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.

Table 1: Fistula Baseline Forms - Forms Completion Schedule

	Forms						
Time							
Prior to Randomization	301	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 the 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 301 and 331. You do not fill out a drop-out form.

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

Forms 301, 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 302 (Fistula Study Dropout Form) if the patient will not be randomized.

Table 2: Fistula Follow-Up Forms - Forms Completion Schedule

	Forms					
	304	305	306	333	334	341
Time						
At Randomization			X			
One day call after randomization: compliance	Enter date on form					
Two week call: compliance/safety	Enter date on form					
Four week call: compliance/safety	Enter date on form					
Six Week Visit	x (complete and enter form)			X	X	X
30 Days after drug discontinued: safety call				X		
Monthly Calls to check on start of dialysis						
Approx. Month 6*		X				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 needs another bottle of study drug, fill out Form 306.

At the 2 week call, 4 week call, 30 day safety call and monthly calls if needed:

Form 333 (Visit), Form 352 (Access Repair/Access Event Procedure), 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 6 week visit if needed:

Form 352, 360, 361, 363, 364, 365, 366, 371, 372

***Approximately at Month 6 (Forms 305 & 341)**

If the patient was on chronic dialysis before the fistula surgery or if the patient was not on chronic dialysis before the fistula surgery but dialysis was initiated within 120 days of fistula creation, forms 305 and 341 are completed between 150 and 180 days after fistula creation.

For patients not on chronic hemodialysis before fistula surgery, if dialysis was initiated more than 120 days after fistula creation, Forms 305 and 341 are completed after 12 consecutive sessions of dialysis treatment, or by 60 days after initiation of dialysis, whichever comes earlier.

For patients whose fistula was abandoned before the six-week visit, complete Forms 304, 333, 334 and 341. For patients whose fistula was abandoned after the six-week visit, complete Forms 305 and 341.

For patients with fistula thrombosis and no restoration of patency during the six week study drug administration period - complete Forms 304, 333, 334, 336, & 341 at the earlier of the following: six weeks after fistula creation or at the end of study participation (30 days after discontinuation of study drug).

After study participation ends:

Before 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, all fistula follow-up forms will have a visit number of "1". If more than one of the same form is filled out for a given patient during follow-up, the visit sequence numbers are incremented from "1" on as needed.

Table 3: DAC Drug Distribution Sites

Center 1 - Boston University Medical Center
Closet 11: Boston Medical Center
Closet 12: Boston Veterans Administration Medical Center
Closet 13: University of Massachusetts Medical School
Closet 14: Brockton Dialysis Center
Closet 16: Taunton Kidney Center

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 36: Covenant 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