CHAPTER 6 FOLLOWUP DATA COLLECTION

6.1 General Principles of Follow-Up

6.2 Determining When a Fistula Will Be Cannulated for the First Time

The person who decides when the AVF will be cannulated for the first time varies from nephrology practices and dialysis units. Very often, the decision lies in the surgeon who performs AVF creation surgery, often following serial post-operative clinic visits. Occasionally, the nephrologist or the vascular access coordinator will be the decision maker. In this context, the physician extender (i.e., nurse practitioner or physician assistant) who works with the nephrologist may substitute for the nephrologist. In some instances, the dialysis unit personnel, such as the dialysis nurse, would make that decision, with or without phone consultation with the surgeon or nephrologist.

For each dialysis unit, the Study Coordinator will find out if there are standing policies that govern (i) the process of making the decision on when the new AVF will be used; (ii) selection of the individual dialysis personnel who performs the initial cannulation; (iii) criteria for selection of the dialysis personnel for the initial cannulation; and (iv) adjustments of needle size and machine pump speed. This information is important to collect for the HFM Study. However, the Coordinator needs to confirm if this policy is indeed followed and who actually makes that decision to cannulate in that particular patient. These data will be collected.

For patients who are already on chronic dialysis, the Coordinator can contact the dialysis unit and/or the nephrologist periodically to estimate the timing of the initial cannulation. The Coordinator should consult the nephrologist to determine if the nephrologist or his/her extender should be contacted for this purpose. The Coordinator should also find out from the dialysis unit whom he/she should contact. This may be the head nurse of the patient's dialysis shift, the nurses or technicians who have been assigned to the patient's dialysis care. It is crucial to remember that there is practically always more than one person in these roles, including the shift head nurse. Therefore, the Coordinator will familiarize himself/herself with multiple staff members who are likely to be involved in the patient's dialysis treatment.

The mode of contact can be phone calls. In most cases, this is the most practical and effective mode. If there are several patients in the dialysis unit who have been enrolled in HFM Study, or if research blood draw at the dialysis unit is necessary on any HFM Study patients, it may be efficient for the Coordinator to physically visit the unit to assess the status of each of the HFM Study patients with one or multiple staff members.

The frequency of this contact varies, depending on the apparent rate of the AVF development. The first contact should not be more than two weeks post-operatively, since that is the time point for a research protocol-mandated ultrasound. Contact should be made every two weeks thereafter, but more frequently if the Coordinator has been informed by any medical personnel that the AVF is developing rapidly, based on clinical observation or other data available to the medical personnel in routine clinical practice. This contact can be as frequent as every dialysis session, if cannulation of the AVF appears imminent.

The Coordinator should also periodically ask the patient if he/she has been informed by any medical personnel about the status of the AVF and whether cannulation appears imminent. This will also help the Coordinator to decide if the frequency of contact with the dialysis unit should

be increased.

For patients who have received AVF placement but who are not yet on chronic dialysis, the collection of these data is more difficult. These patients are seen by medical personnel on a less frequent basis, compared to those who are on chronic dialysis. The nephrologist or the physician extender will make the decision on when the patient will start chronic dialysis. However, the patient may start dialysis using a catheter, while waiting for the AVF to mature. Regardless, the Coordinator should start the contact with the nephrologist or physician extender within two weeks of the AVF placement surgery and maintain contact periodically. The mode of communication will likely be phone or email, depending on the preference of the nephrologist. If email is the mode of communication, it is important to maximize patient confidentiality. The frequency of communication can start with a monthly interval; with a request to the nephrologist to inform you if the patient is starting dialysis. Regardless, the Coordinator should continue to initiate the contact. It is important to find out (i) if a central catheter has been placed during the AVF surgery; (ii) in what dialysis unit the patient is planning to undergo dialysis. If a catheter has been placed, the patient will likely start dialysis within days, or at most 2 weeks. In that case, the Coordinator should start communication with the dialysis unit as soon as dialysis starts, or sooner.

Regardless of communications with the dialysis unit and the medical personnel, periodic direct contact with the patient may be very useful in collecting follow-up data.

6.3 Determining Successful Cannulation

The first cannulation will be confirmed or refuted by contacting the dialysis unit. If possible, the Coordinator should call the dialysis unit by phone the day before the proposed first cannulation, to find out (i) when the dialysis session is scheduled to start; and (ii) who are the likely nurses or technicians who will perform the first cannulation. The dialysis unit may or may not know at that time, but may provide the Coordinator with the name of one or several candidates. The Coordinator should call the dialysis unit an hour after the proposed start time for the patient, in order to ascertain if cannulation has actually occurred, whether the cannulation is successful, and the approximate time that the dialysis session will end.

At 30-120 minutes after the dialysis session is supposed to end, the Coordinator should call the dialysis unit to talk to the person who performed the cannulation in order to obtain the information necessary to fill out form 302. The Coordinator should also obtain or cross-check the information from the dialysis record (the "run sheet") either electronically if available, or the hard copy. The review of the dialysis record should take place preferably on the same day, or at least within 24 hours. If there is a significant delay, it may be difficult to reconcile the data with the dialysis personnel. Discrepancies or suspicious data in dialysis record should be reconciled verbally with the dialysis personnel (the cannulator or the person monitoring the dialysis session).

The following definitions should be followed in the assessment of the cannulation and completion of the study forms:

6.3.1 The First Cannulation Attempt

The first cannulation attempt is defined as the first attempt to cannulate the AVF with at least one needle. If the skin is punctured, regardless of whether or not the vessel is successfully entered, the event should be classified as a cannulation attempt. This definition must be strictly adhered to for this HFM Study.

6.3.2 A Successful First Cannulation

A successful first cannulation is defined as a cannulation of the AVF with two needles and the use of the AVF for the entire dialysis session, regardless of the blood pump speed or duration of the dialysis session. The blood pump speed will be determined by the clinical dialysis staff. The HFM Study Coordinator, investigators and any other HFM Study personnel should have no input on the blood pump speed or any aspects of the dialysis sessions.

6.3.3 First Successful Cannulation with Dialysis Machine Pump Speed ≥300 ml/min.

For the purpose of ascertaining clinical maturation of the AVF, as discussed below, the AVF must be able to support an adequate blood pump speed *or* support an adequate dialysis session (as defined by the laboratory test urea Kt/V). Either definition is acceptable. The urea Kt/V definition is particularly useful for small-sized patients who do not have a large AVF but the AVF is nonetheless sufficient for dialysis by clinical standards. In the first definition, a Successful Cannulation with Dialysis Machine Pump Speed ≥300 ml/min requires (i) cannulation of the AVF with two needles, (ii) use of the AVF for the entire dialysis session; and (iii) a mean dialysis machine pump speed of at least 300 ml/min throughout the dialysis session with the exception of the first hour and last 15 minutes. Dialysis machine pump speeds (mL/min) will be obtained from the dialysis run sheet. The exception for the first hour is provided so that the blood pump speed can be gradually ramped up, which is commonly, practiced in many dialysis units, especially for new AVFs. The exception for the last 15 minutes allows the dialysis staff to draw blood samples for the determination of urea kinetics, as part of routine clinical dialysis care.

6.4 Determining Abandonment

The fistula will be classified as abandoned when it has not been used for a period of at least 2 weeks and the primary nephrologist or surgeon determines that the AVF will not be able to be used in the future for dialysis and that alternative access is required. The determination can be based on clinical, radiologic, or surgical information. It may be made if there is evidence that thrombosis and complete occlusion has occurred or the AVF does not appear to be developing at a reasonable rate after 4-6 months. This decision may be offered spontaneously by the surgeon, nephrologist, physician extender or dialysis staff. Otherwise, the Coordinator should ask one or more of these individuals about the status of the AVF at least on a monthly basis. If there is a discrepancy in opinion, the AVF will not be classified as being abandoned. An AVF that is not used because of patient preference (e.g., patient refuses cannulation) should not be classified as abandoned.

If the AVF is abandoned, the reason(s) for abandonment will be obtained from the primary nephrologist, physician extender or dialysis staff:

1. AVF is too small
2. AVF is too deep to reliably cannulate
3. insufficient length to cannulate
4. frequent infiltration
5. thrombosis of AVF
6. access-related hand ischemia

7. aneurysm or pseudoaneurysm
8. infection
9. venous hypertension
10. cannot achieve desired blood flow rate

If anything has happened to the fistula, including abandonment around the time of the 2-week blood draw, the blood draw is still done. The same is true for any scheduled or required ultrasounds. However, if a physical exam by the surgeon, nephrologist or other trained personnel acceptable to the HFM believes the fistula had clotted within 2 weeks, a 2-week ultrasound does not need to be performed.

Monthly data collection will continue as described below for 3 additional months after the AVF has been abandoned. If an AVF that has been classified as abandoned is used any time during the subsequent 3 months, data collection will proceed from that point forward as if the AVF had not been abandoned.

6.5 Assessing Clinical Maturation

Once the AVF has been successfully cannulated once, a frequent sampling protocol will be implemented as follows, in order to ascertain if the AVF meets the clinical maturation criteria. Clinical maturation is defined as the use of the AVF with two needles for 75% of dialysis sessions within a 4-week period and either A or B:

A. Four consecutive sessions in which the mean blood pump speed is ≥300 ml/min. The four consecutive sessions must occur during the 4-week ascertainment period starting with the First Successful Cannulation and must be sessions in which two needles are used. This is the "blood-pump-speed" criterion.

B. A measured single-pool urea Kt/V ≥1.4 or urea reduction ratio (URR) >70%; either value will be satisfactory. The Kt/V or URR (known as urea kinetic modeling) will be obtained from the clinical dialysis record which is usually performed monthly in most dialysis units. This urea kinetic modeling can occur during any session within the 4-week ascertainment period as long as the AVF is used with two needles. This is the "urea kinetics" criterion.

To ascertain the success of these dialysis sessions, the Coordinator should obtain the information from the electronic version or the hard copy of the run sheet of each of the sessions. The completion of the entire dialysis session can be confirmed by: (i) matching the actual dialysis duration (end time minus start time) and the prescribed duration; or (ii) a note by the dialysis staff in the run sheet stating that the session has been completed. If there is a note stating that the dialysis session has been prematurely terminated, either because of vascular access problem or other problems (such as severe intradialytic hypotension or patient noncompliance), the session will need to be considered a failure from the HFM Study standpoint. If there are uncertainties or discrepancies in the run sheet, the dialysis staff should be contacted for clarification.

<u>If the patient has transferred to a non-HFM approved dialysis unit</u>:

The necessary steps should be taken to include temporary dialysis units as HFM approved units if the patient will be at that unit for >2 months.

Home Hemodialysis Patients

Patients who will be dialyzing at home must have the willingness and skills to complete all necessary data collection. It is up to the discretion of the Principal Investigator whether the necessary data can be obtained.

The patient must be able to complete the Cannulation Form from the first cannulation attempt to the first successful cannulation.

The patient will need to obtain blood pump speed data every 30 minutes from the start to the end of dialysis at every dialysis session from the time of the first successful cannulation until maturation. The Clinical Maturation Form will need to be completed for each dialysis session until fistula maturation assessment is completed.

The Monthly Follow-up Form will also need to be completed monthly from the time of surgery until the end of the study.

Follow-up data collection to assess clinical maturation

1. During the first 4 weeks following the First Successful Cannulation, data should be obtained for every dialysis session according the "Intensive Data Collection Protocol" described below by completing form 305.
2. Starting with the first dialysis session of Week 5, dialysis data should be obtained at each dialysis treatment according the "Intensive Data Collection Protocol" described below by completing form 305, as long as:
    a. the Clinical Maturation criteria have not been met;
    b. the AVF has not been officially abandoned according to HFM Study criteria; and
    c. the AVF has been used for at least one of the preceding 4 dialysis sessions.

If a and b are satisfied but c is not satisfied:

1. At Week 5-12 after First Successful Cannulation, obtain data at one session per week, on the same day every week, according the "Intensive Data Collection Protocol" described below by completing form 305.
2. At Week 13 or later after the First Successful Cannulation, obtain data at one session every two weeks, on the same day every two weeks, according the "Intensive Data Collection Protocol" described below by completing form 305.

Intensive Data Collection (complete Form 305)

At each of the dialysis sessions sampled for "Intensive Data Collection" (i.e., every session, one session per week, or one session per two weeks), the following information will be obtained:

1. Status of study fistula use (see options listed on Form 305)
2. Date of the maturation assessment schedule report in use.
3. Current assessment schedule frequency (from schedule report).
4. Dialysis machine blood pump speed at 30 minute intervals.

If the AVF has been classified as abandoned:

Change to monthly data collection for 3 more months.

It is imperative to enter the dialysis session data into the DCC website as soon as possible, in order for the DCC to determine if the HFM Study definition of clinical maturation has been satisfied. Depending on whether the maturation definition has been satisfied, the dialysis data collection schedule may change. Satisfaction of the maturation criterion can only be determined by the DCC, not the Coordinator or the clinical center PI.

Failure to meet the maturation criteria during an initial 4-week ascertainment period does not preclude the possibility of meeting the criteria during a subsequent ascertainment period. For example, the nephrologist or the dialysis staff may decide to temporarily suspend the use of the AVF because it is tenuous. After the clinical decision to resume the use of the AVF, the Coordinator should notify the DCC immediately, so that another 4-week ascertainment period can be initiated.

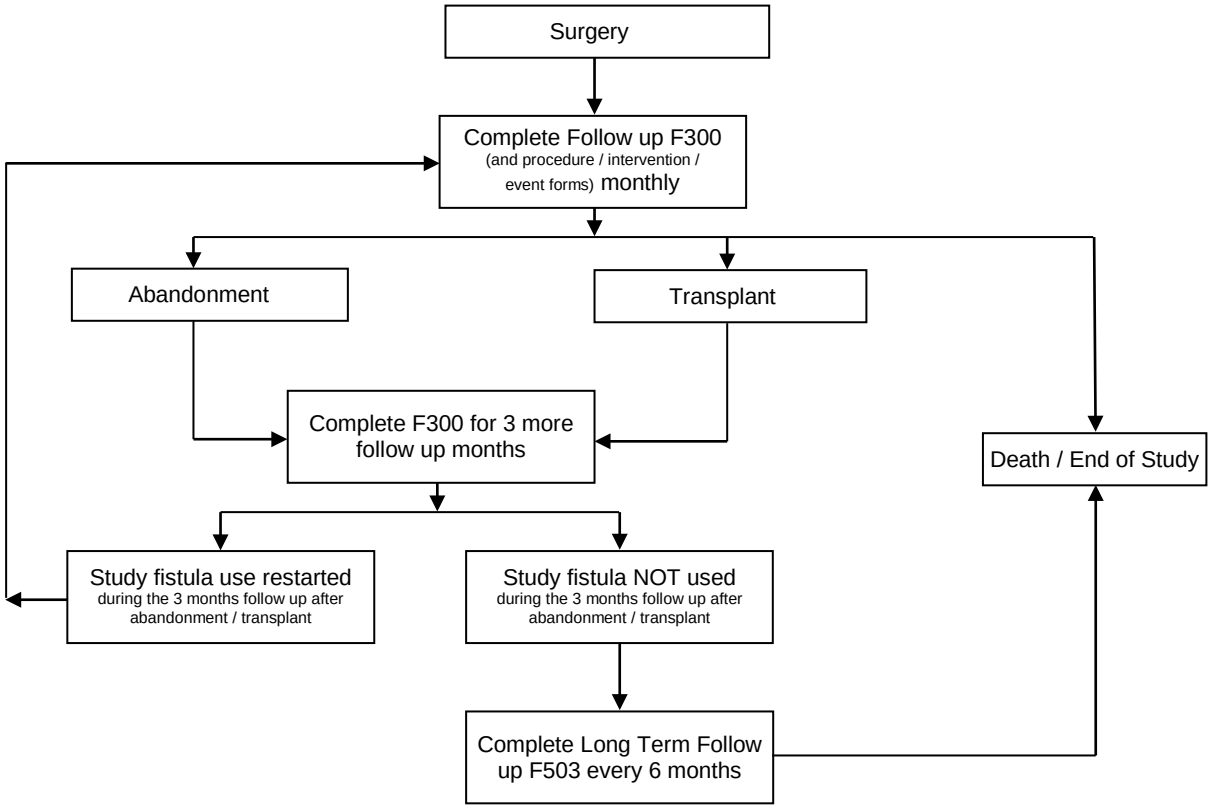
In order to be classified as clinically mature, the AVF will need to satisfy the Clinical Maturation criterion as described above within 9 months after AVF creation for patients already on chronic hemodialysis. For patients who begin dialysis more than 9 months after AVF creation, the 4-week ascertainment period must start within 4 weeks after the initiation of hemodialysis. This 4-week delay allows for an adjustment period for both the patient and dialysis personnel.

After the Fistula Maturation Criteria are met, the following additional information will be obtained every month (complete form 300) until the end of the HFM Study, discontinuation of hemodialysis, confirmed abandonment (3 follow-up months have passed after abandonment and the fistula use has not been restarted), successful transplant (3 follow-up months have passed after transplant and the fistula use has not been restarted), death or end of study follow-up (whichever comes first):

1. Is the AVF being used?
2. Does the patient have a central venous catheter or an arteriovenous graft? Which vascular access is being used?
3. Dialysis adequacy data (obtained from routine clinical urea kinetic modeling and only if the AVF was used): pre-dialysis BUN, post-dialysis BUN, pre-dialysis weight, post-dialysis weight, and duration of treatment session.
4. Fistula events
5. Fistula or other vascular access procedures
6. Adverse events
7. Has the AVF been officially classified as abandoned?

In summary: The patients will need to be followed monthly with a F300 (and the related procedures, interventions and events forms) until one of these 4 events happens:

HFM Study
Monthly Follow up F300 / Long Term Follow up F503 Completions Flow



1. Confirmed abandonment: 3 follow up months have passed after abandonment and the fistula use has not been restarted
2. Successful transplant: 3 follow up months have passed after transplant and the fistula use has not been restarted
3. Death
4. End of study follow up

If the Clinical Maturation criteria are not met within the time frame, the data collection schedule will still proceed as above. This is also true for AVF that do not meet the criteria because the patient does not allow the AVF to be used. If the AVF has been determined by the surgeon and/or nephrologist to be unsuitable for dialysis, data collection will proceed as if the AVF were abandoned.

Follow up after Transplants

If there has been a successful transplant (3 follow-up months have passed after transplant and the fistula use has not been restarted), then follow-up is done every 6 months thereafter (Form 503). The 26 week ultrasound should also be completed if a pre-cannulation ultrasound was never done. If the transplant occurs and the fistula use is restarted after subsequent failure of the transplant, Form 300 data collection will be restarted until one of the 4 events listed above.

6.6 Reports to Guide Data Collection at Study Sites

Daily reports will be available online for each patient to guide the clinical center about the frequency of data collection. Weekly center-specific reports distributed by the Data Coordinating Center will list each subject at the clinical center for whom data should be collected a) at each dialysis session, b) at one session per week, c) at one session every two weeks, or d) at one session per month. Subject-specific reports will indicate the AVF status as: a) clinically mature, b) maturation not yet ascertained, c) failed maturation but AVF not abandoned, or d) abandoned. If AVF maturation has not yet been ascertained, the subject-specific report will indicate whether the fistula has been used for any of the preceding 4 sampled dialysis treatments, and how frequently data should be collected (every dialysis, once per week, once per two weeks, or never).

Generation of daily reports by the DCC requires that the clinical center study team enter data from the prior sampled dialysis session into the database. If the data have not been entered before the next session, the clinical center should follow the sampling schedule on the most recent report. An exception to this will occur if the fistula was used for the most recent sampled treatment and clinical maturation status is not yet determined. In such a case, the fistula use data should be collected at the next dialysis session.